Classification-based Machine Learning Approaches to Predict the Taste of Molecules: A Review

Cristian Rojas[a,*], Davide Ballabio[b], Viviana Consonni[b], Diego Suárez-Estrella[a], Roberto Todeschini[b]

[a] Grupo de Investigación en Quimiometría y QSAR, Facultad de Ciencia y Tecnología, Universidad del Azuay, Av. 24 de Mayo 7-77 y Hernán Malo, Cuenca 010107, Ecuador

[b] Milano Chemometrics and QSAR Research Group. Department of Earth and Environmental Sciences, University of Milano-Bicocca, P.za della Scienza 1-20126, Milano, Italy

[*]Corresponding author. E-mail: crojasvilla@gmail.com

Abstract

The capacity to discriminate safe from dangerous compounds has played an important role in the evolution of species, including human beings. Highly evolved senses such as taste receptors allow humans to navigate and survive in the environment through information that arrives to the brain through electrical pulses. Specifically, taste receptors provide multiple bits of information about the substances that are introduced orally. These substances could be pleasant or not according to the taste responses that they trigger. Tastes have been classified into basic (sweet, bitter, umami, sour and salty) or non-basic (astringent, chilling, cooling, heating, pungent), while some compounds are considered as multitastes, taste modifiers or tasteless. Classification-based machine learning approaches are useful tools to develop predictive mathematical relationships in such a way as to predict the taste class of new molecules based on their chemical structure. This work reviews the history of multicriteria quantitative structure-taste relationship modelling, starting from the first ligand-based (LB) classifiers proposed in 1980 by Lemont B. Kier and concluding with the most recent studies published in 2022.

Keywords

Taste chemistry; Machine learning; Taste classification; QSAR models; Foodinformatics

1. Background

1.1. Taste chemistry

1.1.1. Introduction

Considering the incredible variability of environmental conditions on the planet, the availability of specific foods has played a key role in the adaptive evolution and conservation of species. Indeed, the availability of specific types of nutrition may be one of the most important variables in the evolution of species. Taste and olfaction are the two senses that allow the discrimination of chemical substances (Schieberle & Hofmann, 2016). Dangerous tastes have been empirically correlated with bitterness; however, some of the most ancient medicines include bitter substances (Bayer *et al.*, 2021). Recently, scientific approaches have been replacing empiric ways to understand and to assess the safety of food products. While these scientific approaches have been shown to be useful in the analysis and categorizing of tastes, some foods that are considered safe may illicit, intolerances and allergies in a few people. For instance, human intolerances to gluten and lactose are well known, along with the life threatening anaphylactic allergic response to seafood and peanuts. These relatively rare reactions to food are related to specific digestive enzymes concentrations, and to the human immune system, respectively.

Beyond safety considerations, each person has specific preferences for tastes that can change over one's lifetime. This variation in personal taste preferences could be related to biochemical, as well as environmental, psychological and cultural factors. This diversity of factors makes it difficult to describe the taste mechanisms, e.g. psychologists might consider taste preferences to be related mainly to psychological stimulus, while chemists might think that tastes are perceived primarily through the consequence of chemical reactions that occur in tissues (Behrens & Ziegler, 2020), contributing to kind and intensity of sensations. In this framework, the identification of the healthiest, safest and most preferred foods is of fundamental importance to the food and pharmaceutical industries. Research related to the mechanisms underlying the human perception of tastes is increasing in the last few years (Damodaran & Parkin, 2017). Importantly, current research into tastes and sensory perceptions are being studied from different, but related and interconnected directions, such as chemical, biochemical, anatomical, physiological, and psychological standpoints.

It is common to identify "tastes" or "flavors" as the combination of taste, olfactory, tactile and thermal sensations (Di Lorenzo *et al.*, 2009), while sensomics is the mapping of the combinatorial code of aroma and taste by active key molecules. These molecules are sensed by human chemosensory receptors (Schieberle & Hofmann, 2016). The extraordinary developments in foodinformatics (computational food chemistry) and bioinformatics (computational biochemistry) are providing new tools to assess and to explain the receptor/ligand binding affinity and how the structures of the receptors interact with the chemical structures of the compounds and how to achieve a particular taste of interest (Martinez-Mayorga & Medina-Franco, 2014; Rojas *et al.*, 2016a). At the beginning of sensory research, the greatest efforts were focused on the chemical structure of compounds, their characteristics and the cultural particularities of populations. It was considered that chemical analysis of taste molecules in raw ingredients and in end-products for human consumption could play an important role for the assurance of food quality and desirability preventing defects in products (Ley *et al.*, 2012). However, this approach was not sufficient to explain all the taste phenomena. Later, the importance of the complex anatomy and physiology of taste receptors and how they interact with specific tastant molecules were recognized as key factors to better understand and model the phenomenon of taste.

A molecular tastant is considered to be a water-soluble chemical able to produce taste sensations by activating taste receptor cells (TRCs) and thus activate taste-related pathways at within the nervous system (Di Lorenzo *et al.*, 2009; Rojas *et al.*, 2022). Tastants are elicited not only in water, but also in organic and inorganic acids and amino acids, all of which are able to facilitate the interactions of tastants with receptors (Chaudhari *et al.*, 2009). Chemosensory receptors located in the taste buds of the tongue are fundamental to the regulation of taste sensation. Other mechanisms to recognize molecular tastants are, for example, the opening of ion channels or through secondary messenger channels associated with nucleotides or phosphorylated inositol (Damodaran & Parkin, 2017; Morini *et al.*, 2011; Wong, 2018).

Taste measurement is preferably performed by an experienced panel of assessors. Panelists are trained with standard solutions of the basic tastes by means of the sip and spit methodology (Kelly *et al.*, 2005; Spillane *et al.*, 2006). The concentrations of standard solutions should be prepared at a minimum of their recognition threshold to ensure taste detection (Deng *et al.*, 2021; Liu *et al.*, 2020; Shiyan *et al.*, 2021; Spillane *et al.*, 2006; Yu *et al.*, 2018). The pH of the standard solutions also influences taste perception. Then, a solution of an unknow analyte (generally at concentration of 0.01 M) is provided to members of the panel who are asked to identify the basic taste and aftertaste. The taste potency of the unknown analyte can be estimated by the amount that the solution should be diluted to be equal to the standard. The evolution of technology led to the development of some analytical procedures based on sensors for the sensory evaluation of foods; for instance, electronic noses and tongues, in which their operation is based on the measurement of potential differences that are related to the tastes and aromas that humans can sense (Deng *et al.*, 2021; Liang *et al.*, 2022a; Suárez-Estrella *et al.*, 2021; Xiu *et al.*, 2022).

1.1.2. Basic tastes

Currently, five basic tastes have been identified: sweet, bitter, umami, sour and salty, which are referred to as basic taste modalities, taste qualities or receptor-mediated tastes (Chandrashekar *et al.*, 2006; Damodaran & Parkin, 2017; Di Lorenzo *et al.*, 2009; Morini *et al.*, 2011; Wong, 2018). Among the basic tastes, sweetness is probably the most important one, since sweeteners evoke a high caloric intake and a pleasant sensation in many foods and medicines (Chandrashekar *et al.*, 2006; Damodaran & Parkin, 2017). Most sweet foods contain mono- and disaccharides (Di Lorenzo *et al.*, 2009), which are responsible for their sweetness and quick sources of energy for the body. On the other hand, several non-caloric substances capable of providing a sensation of sweetness to food are currently known and are used in the industry. Those substances may have both natural or artificial origins (Chattopadhyay *et al.*, 2014).

Sweetness perception is related to the presence of a glycophore unit in the sweetener's scaffold. It forms the tripartite model (AH, B and γ units), which interacts with the sweetness receptor along a multipoint attachment (MPA) construct. The sweet taste chemoreceptor is a G-protein coupled receptor (GPCR) of class C composed of the T1R2 (Type 1 Receptor 2) and T1R3 (Type 1 Receptor 3) subunits, which are composed of three structural domains (Chandrashekar *et al.*, 2006; Morini *et al.*, 2011; Wong, 2018). The presence of the AH-B sites in a tastant molecule is a necessary, but not a sufficient condition alone to elicit sweetness; for example, the sweetness taste can be viewed as a function of the size, shape and functionality of the compounds (Spillane & Sheahan, 1989). In other words, a large molecule must be able to fit specifically into the receptor site to generate sweetness. A small molecule with the AH-B site might be unable to match the construct of the receptor site, and the sweet stimulus may not be produced.

Sucrose has a clean (no aftertastes) sweet sensation (even at high concentrations), and consequently it is frequently used as the standard to quantify the relative sweetness (RS) or sweetness potency (Sw) of sweet-tasting molecules (Liu *et al.*, 2020; Rojas *et al.*, 2022; Shiyan *et al.*, 2021; Yu *et al.*, 2018). Sweet potency is defined as the concentration ratio between a sucrose solution standard labeled as 1 (or 100%), and the solution of a sweetener exhibiting the same intensity (iso-sweet concentration) (Rojas *et al.*, 2016a; Rojas *et al.*, 2016b). Sweeteners could be classified as natural (nutritive or carbohydrate) and artificial (non-nutritive or non-carbohydrate) (Ley *et al.*, 2012; Wong, 2018; Yang *et al.*, 2022). On the other hand, certain amino acids and proteins are detected as sweet compounds and some salts taste sweet at low concentrations, including NaCl, KCl, NaOH, KOH, salts of beryllium and lead acetate and carbonate (Di Lorenzo *et al.*, 2009).

Bitterness has been defined as an unpleasant taste. The unpleasant sensation is related to a rejection of some foods, many of which are toxic compounds for humans (Chandrashekar *et al.*, 2006; Di

Lorenzo *et al.*, 2009). Thus, bitter perception might be related to an evolved "alert" system to prevent the intake of high concentration of toxic compounds through food or drink, avoiding their undesirable and potential lethal effects (Ley *et al.*, 2012). On the other hand, not all bitter compounds are toxic and not all toxic compounds are bitter. In fact, some of them have proven beneficial effects for human health, for instance, polyphenols, glucosinolates and terpenes (Bayer *et al.*, 2021). Moreover, some bitter tastes may be perceived as pleasant (Dagan-Wiener *et al.*, 2019) as well as associated food products, such as coffee, beer, olives, and unsweetened chocolate. Plants that are perceived as slightly bitter are commonly used for food, while plants perceived as highly bitter are more commonly used in medicines. Plants perceived as having intermediate bitterness might be used for both alimentation and/or medical purposes (Pieroni *et al.*, 2007; Pieroni *et al.*, 2002).

Bitter molecules generally require the presence of a polar (electrophilic or nucleophilic) group and a hydrophobic group to interact with the bitter receptor. Bitter taste stimuli are associated with 25 receptors (TAS2Rs), which are G protein-coupled (Adler *et al.*, 2000; Chandrashekar *et al.*, 2006; Matsunami *et al.*, 2000). Most of them are located in the same taste receptor cells (TRCs) (Chandrashekar *et al.*, 2006; Damodaran & Parkin, 2017; Di Lorenzo *et al.*, 2009; Wong, 2018). TAS2Rs have not only been identified in the mouth cavity, but also in gastrointestinal, respiratory, reproductive and urinary tract tissues (Bayer *et al.*, 2021). The physiological function of TAS2Rs outside the oral cavity have not been identified. Bitter receptors can be specific for one or a few compounds, while others are able to react to a large number of bitter substances (Di Pizio & Niv, 2015). Some bitter compounds are agonists for some TAS2R subtypes, but antagonists for others (Brockhoff *et al.*, 2011). Bitterness is a common taste reaction to alkaloids and heavy metal salts. Quinine sulfate is the standard used for comparisons among the bitterness of compounds (Dagan-Wiener *et al.*, 2017; Damodaran & Parkin, 2017). Quinine sulfate (Liu *et al.*, 2020; Rojas *et al.*, 2022) and L-isoleucine (Shiyan *et al.*, 2021; Yu *et al.*, 2018) are the most frequently used standards for bitterness identification. Quinine is an alkaloid used in the food industry as a component of some soft drinks to infuse them with bitter taste, for example, tonic water. Substances used as sweeteners, such as sodium saccharine and acesulfame K can become bitter at high concentration and also produce a bitter aftertaste (Di Lorenzo *et al.*, 2009).

Umami is the most recently recognized basic taste. Umami is a Japanese word that means deliciousness. This taste is associated with L-amino acids (such as monosodium glutamate MSG), that are umami enhancers (potentiators) (Baines & Brown, 2016; Damodaran & Parkin, 2017; Suess *et al.*, 2015; Wong, 2018). For instance, MSG exhibits a synergistic effect (enhancement) with the guanosine 5'-monophosphate or inosine 5'-monophosphate nucleotides, although these compounds also show a weak intrinsic umami taste on their own (Ley *et al.*, 2012; Wong, 2018). Also, L-aspartate produces an umami sensation. Umami taste is detected in meats, cheeses, some mushrooms along with fish, kelp and tomatoes. The umami taste stimuli of peptides and their molecular interactions is associated with G-protein coupled receptors (GPCRs) comprised of the subunits T1R1 (Type 1 Receptor 1) and T1R3 (Type 1 Receptor 3) (Liang *et al.*, 2022a; Liang *et al.*, 2022b; Morini *et al.*, 2011). An umami nucleotide binds with the corresponding receptor at three points: two of them are electrophilic (A and B) that interact with the two phosphoryl oxygens and the C6 oxygen, respectively, while site X interacts with the substituent at C2, particularly when the substituent is delocalized (Wong, 2018). The standard used to quantify umami intensity is MSG (Baines & Brown, 2016; Liu *et al.*, 2020; Rojas *et al.*, 2022; Shiyan *et al.*, 2021; Yu *et al.*, 2018).

Sour taste is associated with the presence of organic and inorganic acids in food. Acidity in raw food tends to change with time; for example, acidity in soft fruit decrease as the fruit becomes ripe. A sour taste is associated with unripe soft fruit. Sourness increases also after fermentation processes applied for the production of foods, such as yogurt, wine, vinegar and bread. Initially, sourness perception was related to the capacity of substances to release hydrogen ions in water. However, hydrogen ion release is not the mechanism that produces sourness for organic and diluted inorganic acids (Breslin & Huang, 2006; Roper, 2007). Other mechanisms include proton exchange, a stimulus-gated Ca^{++} channel and the direct entry through an H^+ channel that has not been identified (Di Lorenzo *et al.*, 2009). A sour taste can also be induced by the passage of electric current through the tongue that probably generates hydrogen ions from the hydrolysis of acid or water (Damodaran & Parkin, 2017; Wong, 2018). In addition, undissociated acids play an important role in sour perception. For instance, some weak organic acids that naturally occur in foods, such as citric, succinic, malic, or lactic acid, are perceived to be more sour than hydrochloric acid at the same pH (Ley *et al.*, 2012). On the other hand, other acid molecules (i.e., potassium acid oxalate or protocatechuic acid) exhibit both sour and bitter tastes (Wong, 2018). The standard used to assess the sourness in food is citric acid (Liu *et al.*, 2020; Rojas *et al.*, 2022; Shiyan *et al.*, 2021; Yu *et al.*, 2018).

Saltiness is the sensation produced by some soluble salts, such as those with low molecular-weight, mainly chlorides from sodium, potassium or calcium (Damodaran & Parkin, 2017; Wong, 2018). NaCl is the only compound exhibiting an intense and clean (no after taste) salty taste and it is consequently used as the saltiness standard (Liu *et al.*, 2020; Rojas *et al.*, 2022; Shiyan *et al.*, 2021; Yu *et al.*, 2018). Potassium chloride can be considered a replacement for NaCl, however it can be perceived as a sweet/bitter taste at low concentrations (Di Lorenzo *et al.*, 2009). In contrast, high molecular-weight salts elicit bitter rather than salty taste, such as lithium chloride and ammonium chloride. However, they are limited for human consumption due to safety and their offensive tastes, respectively (Ley *et al.*, 2012; Wong, 2018).

The physiological function of the salty taste is to maintain the body's electrolyte balance. In taste buds, ion channels allow the passage of chemical species that trigger stimuli perceived as salty, and there is a relationship between the number of fungiform papillae and sensitivity to salty taste (Doty *et al.*, 2001). Apparently, the salty taste is related to the body's ability to detect sodium, thanks to the specific transduction mechanism of this cation, and its passage through the epithelial-sodium channel (ENaC) in the apical membrane of the receptor cells of taste. The epithelial-sodium channel is the mammalian Na^+ specific taste receptor. Most mammals have at least one type of salt taste receptor that is cation nonselective, apparently from the salty taste evoked by KCl and NH_4Cl molecules. At the same time, high circulating aldosterone levels suggest aldosterone modulated epithelial cell membrane Na^+ transporters as candidate for salt taste receptors (DeSimone & Lyall, 2006). Moreover, one or more receptors, such as a variant of TRPV1 (TRPV1t), may be able to respond to various cations including K^+, Ca^{2+}, NH_4^+ and to Na^+ (DeSimone & Lyall, 2006; Rhyu *et al.*, 2021).

1.1.3. Non-basic tastes

Some compounds or combinations of compounds can produce tastes considered as non-basic or secondary tastes, such as astringent, chilling, cooling, heating and pungent (Damodaran & Parkin, 2017; Ley *et al.*, 2012; Wong, 2018). Moreover, other sensations have also been described as non-basic tastes, such as fattiness, or the definition of water as a tastant. Other characteristics of substances have led to the classifications of compounds as multitastes, taste modifiers or tasteless.

The definition of fattiness as a taste has been triggered by the transduction mechanisms that are sensitive to fatty acids in the TRCs membranes (Gilbertson *et al.*, 1997). The transduction mechanisms are associated with the inhibition of delayed rectifying K^+ channels and through the fatty acid CD36 (Di Lorenzo *et al.*, 2009). Evidence suggests that fatty acids (e.g. linoleic acid, oleic acid and stearic acid) could be considered as tastants and that their tastes are detectable without the need for other sensory cues such as texture, viscosity or smell (Di Lorenzo *et al.*, 2009). On the other hand, water has its own taste, even though it could be affected by temperature and easily affected by diluted compounds even at low concentration. Moreover, it could be considered as a tastant because of the role of water in eliciting compounds in TRCs and in taste nerves of some species (Di Lorenzo *et al.*, 2009). It has been suggested that an aquaporin, AQP5, a membrane channel, allows the water molecules to get into the cell by activating and regulating the volume of water through the anion channel (Di Lorenzo *et al.*, 2009). Moreover, when the mouth is rinsed after the application of a sweet taste blocker, water elicited a sweet aftertaste (Di Lorenzo *et al.*, 2009).

Multitaste is a complex sensation of tastes elicited by combining more than one basic taste at the same time (Rojas *et al.*, 2022). It is triggered by a variety of different compounds. Some examples of multitaste compounds are the potassium acid oxalate and protocatechuic acid, which produce sour/bitter tastes (Wong, 2018), calcium phenolsulfonate (bitter/astringent tastes) and benzyl acetate (bitter/pungent tastes) (Dagan-Wiener *et al.*, 2019). Some compounds are able to alter and even block the taste of other compounds. Na^+ channel blockers reduce the saltiness of sodium chloride, thaumatin and adenosine monophosphate block bitterness, while lactisol proprionate blocks sweetness. On the other hand, some compounds increase the taste of others (taste enhancers); for example chlorogenic acid and cynarin enhance the sweetness (Di Lorenzo *et al.*, 2009). In contrast, some compounds have antagonist effects, that is, they tend to suppress the taste sensation of other compounds. This is what occurs with citric acid and sucrose tastants in lemonade. It is also possible to find synergistic effects, for instance the enhancement of umami taste by the addition of IMP or GMP to MSG (Di Lorenzo *et al.*, 2009).

The expression "tastelessness" is used to categorize molecules as lacking any particular taste. These are also classified as non-sweet, non-bitter, non-sour, non-salty or non-umami compounds (Rojas *et al.*, 2017; Rojas *et al.*, 2022). Some changes in the chemical structure of substances may modify their sweet taste to a bitter one or make them tasteless. For example, the saccharin sweetener becomes bitter by the introduction of a nitro group onto carbon five (5-nitrosaccharin), while the introduction of this group on the four-carbon position produces a sweet/bitter tastant (*p*-nitrosaccharin). On the other hand, the presence of the amino group produces a sweet/tasteless compound (6-aminosaccharin) or a tasteless molecule (5-aminosaccharin) (refer to Figure 1) (Rojas *et al.*, 2022). Interestingly, some tasteless compounds like miraculin and circulin act as taste modifiers, in particular, these compounds change the sense of sour in substances to sweet. In contrast, gymnemic acid, ziziphin and hodulcin block the sensation of sweetness (Di Lorenzo *et al.*, 2009).

Figure 1 should be inserted around here

1.2. Machine learning to uncover Structure-Taste Relationships

Studies of Quantitative Structure-Property Relationships (QSPRs) enhance the definition of mathematical relationships between molecular structures and specific properties of chemical compounds, such as taste. These approaches have played an important role in the evaluation and study how molecular features are related to the taste of chemical substances through the development of empirical data-driven models. QSPR models require molecular descriptors, which are numerical indices that encode the detailed chemical and structural information of molecules. They can be both experimental physicochemical properties of molecules and theoretical indices, which are calculated through mathematical algorithms (Todeschini & Consonni, 2009). Molecular descriptors are used as independent variables in QSPR models. The relationships between descriptors and the property of interest (e.g., the taste of chemicals) are calculated by means of chemometrics and machine learning approaches.

The QSPR workflow starts with an appropriate description of the molecular structures and ends with the prediction of the behavior of the chemicals. This approach relies on the assumption that the molecular structure of a substance encodes the chemical features that are responsible for its physical, chemical, and biological behavior. If these features are correctly encoded into numerical descriptors, then QSPR strategy allows first to establish the empirical relationships between descriptors and the property of interest by means of statistical multivariate modeling, and subsequently infers the property of a new substance or untested chemical through the QSPR model.

There are several multivariate statistical methods to process molecular descriptors and achieve reliable estimates of chemical properties. Depending on the nature of the modeled property, classification and regression methods can be used to calculate models both for reproducing the known experimental data and predicting the unknown data for qualitative and quantitative responses, respectively. If chemicals belong to defined qualitative classes; for example, molecules labelled as positive or negative, then supervised classification models can be applied. Classification approaches define mathematical relationships between descriptors and classes and can thus be used to predict the class of new substances that are associated with unknown experimental class labels. If chemicals are associated with a quantitative response, regression methods are used to define the mathematical model that relates descriptors and the response to obtain quantitative predictions for new chemicals.

The two main operational steps in the development of QSPR models are the definition of their applicability domain and the implementation of proper validation protocols, as proposed by the OECD (Organization for Economic Co-operation and Development) in the framework of the five general principles for QSARs (Gramatica, 2007). These principles are used as the criteria to evaluate and accept QSPRs, especially for regulatory purposes, and state that each model should have: 1) a defined endpoint; 2) an unambiguous algorithm; 3) a defined domain of applicability; 4) appropriate measures of goodness-of-fit, robustness and predictivity; 5) a mechanistic interpretation, if possible.

The Applicability Domain (AD) of a QSPR model is the chemical space where predictions can be considered as reliable (Mathea *et al.*, 2016; Sahigara *et al.*, 2012). If the properties of a new untested molecule are predicted through QSPRs, then it is considered to share the same mechanisms and/or modes of action as the molecules used to build the model provided that it is structurally similar to the training molecules and falls inside the AD. In this case, the properties of predicted chemical are considered as interpolated by the model and its predicted properties can be assumed to be reliable. In contrast, the predictions for molecules falling outside the AD can be considered as model extrapolations, and consequently they are considered to be unreliable.

Moreover, the attention to effective and reliable estimates through predictive models has a crucial role in the QSPR workflow. When supervised qualitative (classification) or quantitative (regression) approaches are used to establish structure-property relationships, the primary goal of the process is to achieve reliable models that are able to correctly predict the properties of new untested molecules. QSPR modeling could also have explanatory purposes, that is, allowing the interpretation of the relationship between descriptors and the modeled property to deepen the knowledge about the specific problem in analysis. In both cases, validation protocols for the assessment of the predictive ability of models and the reliability of the established relationships should be always applied (Oliveri, 2017; Wold & Eriksson, 1995). This step is necessary also to avoid overfitted models, that is, models in which mathematical relationships accurately predict properties for the training compounds, but not for new untested substances.

The predictive abilities of the models are usually evaluated by splitting the available compounds into training and test sets. Training compounds are used to establish the mathematical model, which is then used to predict the responses of the chemicals included in the test set. Finally, the agreement between of experimental and predicted responses for the test substances is evaluated to assess the model's predictive ability. Several validation protocols exist and the usage of a particular one usually depends on how many chemicals are available for model development. A general requirement is that molecules in the test chemical space should be reasonably similar to that of the training space. However, large degrees of similarities could produce an excessively optimistic evaluation of a model's predictive ability. For this reason, when dealing with classification models, it is preferable to keep the class balance equal in the training and test sets; that is, the same distribution of chemicals in the modeled classes should be preserved in both sets.

1.2.1. Classification approaches

In the framework of machine learning applied to QSPR, classification methods are fundamental techniques aimed at finding mathematical relationships that recognize the class membership of molecules on the basis of a set of molecular descriptors. Once a classification model has been trained, the membership of unknown chemicals to one of the defined classes can be predicted. Thus, for discrete molecular properties, like qualitative properties distinguishing between different tastes, a general representation of classification models is the following:

$$C = f\left(x_1, x_2, \ldots, x_p\right) \quad (1)$$

where C is the class, x_1, ..., x_p are p (number) of molecular descriptors, and f is a function representing the relationship between the class and the descriptors.

Several classification methods have been proposed in the last decades, with different characteristics, advantages and limitations (Lavine & Rayens, 2009). A preliminary distinction among classification methods can be defined on the basis of the mathematical form of the decision boundary: linear methods calculate the best linear boundary for class discrimination, while non-linear methods discriminate classes by non-linear boundaries.

Another important difference can be made between discriminant (pure classification) and class-modeling methods. Discriminant methods divide the whole chemical space defined by the molecular descriptors in as many regions as the number of the modeled classes. Thus, each compound is assigned the class corresponding to the region of the chemical space where it falls. On the other hand, class-modeling methods (also known as one-class classifiers) define the boundary to separate a specific class from the rest of the chemical space. Thus, a target class is modeled independently of the others; compounds fitting the class model are considered members of the class, while chemicals that are outside the class space are classified as non-members of the target class.

Among classification methods, Discriminant Analysis (DA) is the most widely used (Hand, 1997; McLachlan, 1992). DA finds the directions in the multivariate space that maximizes the ratio of the between-class to within-class variances; these are called discriminant functions and from a mathematical point of view, these directions are linear combinations of the original variables. Depending on the choice of the class-covariance representation, two different discriminant methods can be distinguished: Quadratic Discriminant Analysis (QDA) and Linear Discriminant Analysis (LDA), which define quadratic and linear boundaries between classes, respectively. One major drawback for DA is that it cannot be applied to datasets with the number of samples lower than the dimension of the measurement space. However, to overcome this limitation, DA can be combined with methods for dimensionality reduction, such as variable selection approaches or principal component analysis (PCA).

Another option to deal with highly dimensional spaces is the application of Partial Least Squares Discriminant Analysis (PLSDA) (Barker & Rayens, 2003; Brereton & Lloyd, 2014). PLSDA benefits from the properties of PLS (Partial Least Squares) regression, since it searches for the latent variables, that is, the directions of maximum covariance with the response to be modeled. The difference from PLS is that the response encodes class membership with binary codes and class thresholds have to be defined to predict samples in one of the modeled classes.

Unlike DA and PLSDA, which are discriminant classifiers, the Soft Independent Modeling of Class Analogy (SIMCA) method is one of the most useful and popular class-modeling approaches. It is based on PCA carried out on the samples of the target class. To predict the class of test samples, the sample distances from the class PCA model are calculated on the basis of normalized Q residuals and Hotelling's T^2 values, which measure how well each sample conforms to the model. Only samples with distances lower than a defined threshold are classified into the class space.

Another class modeling approach consists of the calculation of Potential Functions (PFs), where the assignment of a new sample to the target class is based on the cumulative potential of the class, which is calculated as the sum of the individual potentials of the target class samples in the point of the chemical space where the new sample is projected. The shape of the potential depends on the choice of the type of potential function (kernel) and smoothing parameter (Brereton, 2011).

Tree-based algorithms exploit different classification approaches. They recursively divide data into smaller subgroups, which contain samples belonging to as few classes as possible. In each split, the partition is achieved by maximizing the purity of the new subsets. The final classification model consists of a collection of nodes that define the classification rule. One of the most common tree-based approaches is the Classification and Regression Tree (CART), which selects the variables that provide the purest subsets of samples in each node (Breiman *et al.*, 1984). The Random Forest (RF) method represents a subsequent development of tree-based approaches (Breiman, 2001). It is a meta-classifier based on an ensemble of classification trees, each trained on various subsamples of the training set, which are built by bootstrapping. The prediction is then obtained by majority vote among the classifications provided by the trees of the forest.

Another approach, based on the ensemble of models, is AdaBoost (Adaptive Boosting), where predictions provided by many "weak" classifiers are pooled to produce a better classification. Predictions are combined through an adaptive iterative algorithm that exploits the weighted majority voting (Freund & Schapire, 1997). Besides the original boosting method, other approaches have been proposed and applied for the prediction of molecular taste, especially when dealing with big datasets, such as XGBoost (eXtreme Gradient Boosting) (Chen & Guestrin, 2016). This is again a classification algorithm that uses sequential iterations, where decision trees are combined to increase classification accuracy.

Often QSPRs exploit similarity-based classification, since compounds with similar molecular structures are expected to have similar properties. These methods calculate distance measures to provide a classification in terms of similarity among samples. The most known approach in this framework is the *k*-Nearest Neighbors (*k*NN) classifier: it classifies a sample according to the most frequent class of its *k* most similar training samples (Kowalski & Bender, 1972). The N3 (*N*-Nearest

Neighbors) approach is an evolution of *k*NN, which uses locally-weighted information to classify new samples. The Binned Nearest Neighbors (BNN) method is similar to *k*NN, but the prediction is based on a flexible number of neighbors (Todeschini *et al.*, 2015a).

Another classification approach, which is relatively frequent in QSPR applications, is the Support Vector Machine (SVM) method (Vapnik, 1998). It defines the boundary between two classes by maximizing the distance between the support vectors and the decision boundary, where support vectors are those training samples located in the proximity of the class border. Moreover, SVM can use non-linear kernel functions for defining non-linear decision boundaries.

To visually exemplify the different ways classification methods can define boundaries between classes, a dataset of 324 chemicals was generated from the ChemTastesDB database (Rojas *et al.*, 2022), including 61 chemicals labelled as sweeteners and 263 as bitterants. Their molecular structures were encoded through the binary molecular access system (MACCS) keys (Durant *et al.*, 2002). The chemical space was represented by the first two t-Distributed Stochastic Neighbor Embedding (t-SNE) dimensions (van der Maaten & Hinton, 2008), calculated by using the Jaccard-Tanimoto metric as the distance measure (Todeschini *et al.*, 2015b). Finally, different classification approaches were calculated to show how the class boundaries can vary in a 2D space according to the adopted method (Figure 2). SIMCA and PFs, which are class-modeling approaches, define a boundary around the target class (sweet class in this example), while the discriminant methods, for instance, LDA, QDA and PLSDA, divide the entire chemical space into two sub-spaces, each associated with one of the two modeled classes, with linear or non-linear boundaries, depending on the adopted classification algorithm.

Figure 2 should be inserted around here

1.2.2. Classification measures

QSPR models must be assessed through measures of goodness-of-fit and goodness-of-prediction. In this framework, several indices can be used to evaluate the quality of models, which are based on the number of misclassifications (molecules assigned to the wrong class) (Ballabio *et al.*, 2018). Classification metrics are derived from the confusion matrix, which is a square matrix with dimensions $G \times G$, where G is the number of modeled classes. Each entry c_{gk} of this matrix represents the number of samples belonging to class g and assigned to class k. Consequently, the diagonal elements c_{gg} denote the counts of the correctly classified samples while the off-diagonal elements represent those erroneously classified. In the simplest binary case where two classes (positive and negative) are modeled, the confusion matrix is a 2 × 2 numerical table with four entries labelled as follows: true positive and true negative (TP and TN, the number of positive and negative samples correctly classified, respectively), false positive (FP, the number of negative samples classified as positive) and false negative (FN, the number of positive samples classified as negative).

The most common classification measures derived from the confusion matrix are *sensitivity* (Sn_g), *precision* (Pr_g), *specificity* (Sp_g), as well as their combination, such as the *F-score* (F_g) (also known as the *F_1-score* or *F-measure*). These indices are associated to each modeled *g*-th class and defined as:

$$Sn_g = \frac{c_{gg}}{n_g} \qquad Pr_g = \frac{c_{gg}}{n'_g}$$
$$Sp_g = \frac{\sum_{\substack{k=1 \\ k\neq g}}^{G}\left(n_k - c_{kg}\right)}{n - n_g} \qquad F_g = 2\cdot\frac{Sn_g \cdot Pr_g}{Sn_g + Pr_g} \tag{2}$$

where n_g is the number of samples of the *g*-th class, n'_g is the number of samples that are classified in the *g*-th class and *n* is the total number of samples. Higher values of sensitivity, specificity and precision are associated with better class discrimination.

Beside measures assigned to each class, global classification indices have been proposed to provide an overall assessment of the discrimination ability of classifiers. The *Non-Error Rate* (*NER*, also called *balanced accuracy* or *recall*) corresponds to the arithmetic mean of class sensitivities:

$$NER = \frac{\sum_{g=1}^{G} Sn_g}{G} \tag{3}$$

while *accuracy* corresponds to the fraction of correctly classified samples:

$$ACC = \frac{\sum_{g=1}^{G} c_{gg}}{n} \tag{4}$$

Note that accuracy is considered a biased estimate when classes are unbalanced, that is, samples are distributed in classes with significantly different frequencies.

Alternatively, classification performance can also be evaluated through the Matthew Correlation Coefficient (*MCC*), which ranges between -1 and 1 and has originally been defined to assess binary classification tasks:

$$MCC = \frac{TP \cdot TN - FP \cdot FN}{\sqrt{(TP+FN)\cdot(TP+FP)\cdot(TN+FP)\cdot(TN+FN)}} \qquad (5)$$

Another way to assess discrimination capability of classification models is through ROC (Receiver Operating Characteristics) curves. These are graphic plots of *sensitivity* and 1 - *specificity* (also known as False Positive Rate, FPR) for a classification system when its discrimination threshold is changed. For each threshold value, the corresponding TPR and FPR values are calculated. The optimal classifier will provide a full ROC curve, while a random classification rule would give a line along the diagonal of the ROC space. To quantitatively compare classification models trough ROC curves, a common approach is to calculate the area under the curve (*AUC*), also known as *AUROC* or *ROC-AUC*.

2. Classification models for taste prediction

In this section, ligand-based (LB) classifiers for taste prediction are described. The classifiers were retrieved from 52 published studies, which were found through critical screening of the Web of Science citation indexing service. To the best of our knowledge, the first work published on this topic was by Lemont B. Kier in 1980. In addition to the models described below, there are several multicriteria reviews that are focused on QSAR-based prediction of tastes by means of diverse classification-based machine learning approaches (De León *et al.*, 2021; Malavolta *et al.*, 2022; Rojas *et al.*, 2016a; Spillane *et al.*, 1996; Walters, 2006). Ligand-based models are presented on the basis of the basic tastes to be predicted.

2.1. Sweet and bitter tastants

The discrimination between sweet and bitter compounds has probably been the most important task in quantitative structure-taste relationship studies. Twelve ligand-based (LB) models for the discrimination of these two tastes are summarized in Table 1.

Table 1 should be inserted around here

Earlier studies had been focused on the use of simple modeling approaches, such as discriminant analysis. In 1980, Kier (Kier, 1980) performed a two-variable linear discriminant analysis (LDA) to discriminate sweet and bitter aldoximes taken from the data published by Acton and Stone (Acton & Stone, 1976). For each class, 10 tastants were selected on the basis of the largest percentage of the taste and the most potent taste response. Each molecule was represented by two connectivity indices named ${}^{1}\chi$ and ${}^{4}\chi_{p}$. The classifier was used to predict the taste of nine external molecules, achieving seven correct predictions, one incorrect prediction and one tastant labelled as ambiguous. After this pioneering work, Takahashi and Miyashita's group (Miyashita *et al.*, 1986a; Takahashi *et al.*, 1984; Takahashi *et al.*, 1982) developed new models, based on LDA and SIMCA. In the first study (Takahashi *et al.*, 1982), three molecular descriptors were used to correctly classify 22 perillartines (11 in each class) through a LDA classifier. In a subsequent study (Takahashi *et al.*, 1984), a test set of nine compounds (five sweet and four bitter) retrieved from Acton's dataset (Acton & Stone, 1976) was included. Two LDA classifiers, one based on three descriptors and one with just two descriptors, were developed, achieving similar performances on both training and test sets. In the last study, Miyashita (Miyashita *et al.*, 1986a) used 70 sweet and 21 bitter aspartyl dipeptides (L−Asp−NH−R) to calibrate a five-variable SIMCA model.

Drew (Drew *et al.*, 1998) used a dataset of 21 sweeteners, 20 sweet/bitter and 9 bitter mono- and di-substituted sodium sulfamates, which were properly optimized by the semiempirical PM3 method to calculate 11 molecular descriptors. Then, they performed a discriminant analysis (DA), which was able to perfectly discriminate all the compounds. In addition, a cluster analysis was carried out in the space of the first two principal components, where a linear separation could be found only between sweet and sweet/bitter tastants. Two years later, Spillane (Spillane *et al.*, 2002) synthetized and characterized 23 meta-phenylsulfamate derivatives. The equilibrium geometry of the tastants were obtained by means of the AM1 semi-empirical method, in such a way as to calculate diverse descriptors, which were used to calibrate a discriminant plot, an LDA and a quadratic discriminant analysis (QDA). The first model was obtained by plotting the values of length (x, Å) against the volume V_{CPK} (xyz, Å^3). The best LDA classifier was obtained with the x, width (z, Å), aqueous solvation energy (E_{solv}) and HOMO descriptors; while the best QDA model used the x, z, E_{solv} and LUMO descriptors. Among these models, the QDA exhibited the best performance in terms of the *NER*. In a further analysis, these three models were used for predicting the taste of 9 unsynthesized meta-compounds.

Other models to discriminate sweetness and bitterness were based on the *k*-Nearest Neighbors (*k*NN) approach. The first model was proposed by Takahashi (Takahashi *et al.*, 1982) to classify 22 perillartines. The *k*NN method misclassified only two bitter molecules in the entire dataset. Several years later, *k*NN was used by Rojas (Rojas *et al.*, 2016c) with 508 curated and filtered tastants (427 sweet and 81 bitter), which were split into training (356 tastants) and test sets (152 molecules). Molecules were represented by means of 3,763 conformation-independent Dragon molecular descriptors (Kode srl., 2018), which were initially analyzed by means of the V-WSP unsupervised variable reduction approach (Ballabio *et al.*, 2014). Then, the training set was used for model development using the 5-fold cross-validation approach to determine the optimal *k* value during the genetic algorithms-variable subset selection (GAs-VSS). A four-descriptor model was selected as optimal, with a balanced performance in prediction (*NER* = 0.789, Sn_{sweet} = 0.953 and Sn_{bitter} = 0.625). In addition, the applicability domain (AD) of the model was calculated. In a further analysis, the sweeteners database was used to perform a quantitative structure-property relationship (QSPR) for predicting the relative sweetness (RS) or sweetness potency (Sw) of the sweeteners (Rojas *et al.*, 2016b).

Starting from 2017, the random forest (RF) classifier started to be applied to discriminate sweet and bitter tastants. Chéron (Chéron *et al.*, 2017) merged 316 sweeteners from SweetenersDB and 680 bitterants from the BitterDB (Wiener *et al.*, 2012), which were represented by 244 conformation-independent Dragon descriptors (Kode srl., 2018). One hundred trees with a tree depth of five molecular descriptors and the Gini splitting criterion were set up during the calibration of the RF classifier, which exhibited good performance on the test set, constituted by the 20% of tastants (*NER* = 0.914 and *MCC* = 0.848). In a further analysis, the model was used to identify 4,585 natural molecules of the SuperNatural II database (Banerjee *et al.*, 2015) as potential sweet agents and their relative sweetness was predicted by means of a support vector regression (SVR). One year later, Banerjee and Preissner (Banerjee & Preissner, 2018) calibrated a RF model, named BitterSweetForest, for 517 sweeteners from SuperSweet (Ahmed *et al.*, 2011) and 685 bitterants from the BitterDB (Wiener *et al.*, 2012). Compounds were represented by means of the extended connectivity fingerprints ECFP4 (Morgan, 1965; Rogers & Hahn, 2010) calculated using RDKit. The best model achieved good predictive ability of the 241 test set molecules (*AUC* = 0.98, *F-score* = 0.92, *ACC* = 0.967, and *Cohen's Kappa* = 0.92). In addition, the BitterSweetForest model was used to virtually screen the SuperNatural II (Banerjee *et al.*, 2015) and DrugBank databases. Goel (Goel *et al.*, 2021) developed a dataset of 1,179 sweeteners and 743 bitterants (retrieved from the BitterSweet database (Tuwani *et al.*, 2019)) and used the recursive feature elimination approach to identify eight descriptors from 1,613 conformation-independent Mordred descriptors (Moriwaki *et al.*, 2018). The best RF classifier exhibited good prediction on the test set (20% molecules), with *NER* = 0.855, *ACC* = 0.865 and *MCC* = 0.785. In addition, 478 structurally diverse sweeteners (334 in the training set and 144 in the test set) were used to predict the relative sweetness (log RS) by means of a 3D regression-based RF model, which was then submitted to a molecular docking simulation to calculate the binding conformation and associated free binding energy with the T1R2/T1R3 receptor. In a subsequent step, compounds from the Universal Natural Products Database (UNPD) (Gu *et al.*,

2013) were virtually screened following the above mentioned workflow, which was coupled with toxicity scaffold analysis as well.

Recently, other advanced classifiers were used for sweetness and bitterness discrimination. In 2022, Bo (Bo *et al.*, 2022) curated a dataset of 797 bitterants and 1,249 sweeteners retrieved from the BitterDB (Dagan-Wiener *et al.*, 2019), SuperSweet (Ahmed *et al.*, 2011) and FlavorDB. The 2D RDKit molecular descriptors and fingerprints were used to calibrate multilayer perceptron (MLP) models, while 2D-RGB color images (32 × 32 pixels) were used to train convolutional neural networks (CNN). Among the three models, the best one (BitterSweetMLP-Fingerprint) was obtained with 17 fingerprints (selected by means of the PCA using oblique rotation), with good performance for predicting the 409 test set tastants (*NER* = 0.880, *AUC* = 0.950, *ACC* = 0.880, and *MCC* = 0.750). Molecular charges and their surface interaction descriptors were retained since they were relevant for classifying sweeteners/bitterants. Maroni (Maroni *et al.*, 2022) calibrated a gradient boosting machine model (LightGBM implementation), along with other well-known classifiers: *k*NN, RF, logistic regression (LR) and multilayer perceptron (MLP). These authors filtered and curated a database of 2,195 tastants, which were represented by 1,402 conformation-independent features calculated in the RDkit, Pybel (O'Boyle *et al.*, 2008) and Mordred (Moriwaki *et al.*, 2018). A sequential descriptor selection combined with hierarchical clustering in the descriptor’s Spearman rank-order index was used. The GBM classifier was optimal with good results in calibration (*NER* = 0.893, *AUC* = 0.950 and *F-score* = 0.883). Furthermore, the SHapley Additive exPlanations (SHAP) allowed the identification of the most suitable descriptors.

2.2. Sweet and non-sweet tastants

Several classification-based machine learning models have been built to discriminate between sweet and the non-sweet molecules, as well as to use them in order to predict and synthesize novel sweeteners. Nineteen ligand-based classifiers for sweet taste predictions are summarized in Table 2.

Table 2 should be inserted around here

As presented in the sweet/bitter section, the sulfamate sweetness prediction was based on models using biplot discriminant analysis (DA) published mainly by Spillane’s research group. In the first application, Spillane and McGlinchey (Spillane & McGlinchey, 1981) used the length (*x*, Å) and volume V_{CPK} (xyz, Å^3) descriptors to construct a DA-biplot for the discrimination of 47 sweet and non-sweet carbosulfamate ($\mathrm{RNHSO_3^-}$) derivatives. In a second study, Spillane and Sheahan (Spillane & Sheahan, 1989) again used the *x* and V_{CPK} descriptors to classify 17 carbosulfamates. In a subsequent DA-plot application (Spillane *et al.*, 1993), the V_{CPK} and $\Sigma\sigma$ descriptors were used for 40 synthesized ring disubstituted phenylsulfamates as sodium salts (no classification performances were reported for this discriminant plot). Between 1983 and 2009, the same research group developed six models based on linear discriminant analysis (LDA) and four models based on quadratic discriminant analysis (QDA). In the first LDA application, 33 sweet and non-sweet heterosulfamates were used (Spillane *et al.*, 1983). Twenty molecules were retrieved from the Acton's database (Acton & Stone, 1976), while another 13 tastants were synthesized and evaluated by the authors for taste sensation. The best model was composed of the length (*x*, Å), width (*z*, Å) and the first-order valence connectivity index (${}^{1}\chi^{v}$) descriptors. In a subsequent study, Spillane and Sheahan (Spillane & Sheahan, 1989) used the same pool of descriptors to calibrate a LDA model for other 23 heterosulfamates and an extended dataset of 56 heterosulfamates.

Starting from 2000, the classification and regression tree (CART) method was also used for sweetness prediction. Spillane (Spillane *et al.*, 2000) augmented previous datasets in order to include 101 heterosulfamate sodium salts (32 were synthesized for this study). The datasets contained 20 sweeteners and 81 non-sweet derivatives. LDA and QDA models were calibrated with four molecular descriptors (*x*, *y*, *z* and and ${}^{1}\chi^{v}$), while with CART, three features were used (*x*, *y* and ${}^{1}\chi^{v}$). Among these models, the QDA classifier showed the best performance. Three years later, the dataset was further augmented by including newly synthesized compounds (15 sweet and 16 non-sweet) (Spillane *et al.*, 2003). In this case, CART provided better results than LDA and QDA using the *y*, *z*, V_{CPK} and LUMO descriptors. In 2005, Kelly (Kelly *et al.*, 2005) merged 63 sweeteners available in the literature with 19 cyclamate derivatives that were synthesized and tasted in this work. The sweetness value was used to define three classes of the predominant tastes: non-sweet (0 to 39), sweet/non-sweet (40 to 60) and sweet (61 to 100). The dataset was randomly split (maintaining the class proportion) into a training set and a test set of 75 molecules and 8 molecules, respectively. In this work, an external validation was used for the first time for the sweet/non-sweet discrimination. The LDA and QDA models exhibited poor predictive ability, while CART based on six descriptors (*x*, HOMO, LUMO, E_{solv}, $V_{Spartan}$ and σ) exhibited acceptable prediction performance.

One year later, Spillane (Spillane *et al.*, 2006) developed three CART models to study a dataset of 82 tastants (42 newly synthesized disubstituted phenylsulfamates). The best classifier used 70 molecules in the training set and 12 test set compounds randomly selected. Molecules in the test set were only the newly synthesized non-sweet (11 compounds) and sweet/non-sweet (1 compound), while the four newly synthesized sweeteners were placed in the training set. This model used seven descriptors and provided good prediction ability. Finally, 28 five-membered aromatic ring thiazolyl-, benzothiazolyl-, and thiadiazolylsulfamates were synthesized and merged together with 30 well-known heterocyclic sulfamates to create a database (Spillane *et al.*, 2009). Compounds were grouped into three classes according to the predominant taste: sweet, non-sweet and sweet/non-sweet. LDA and QDA were initially used considering all the molecules as training chemicals. Then, the authors calibrated two CART models by randomly splitting the dataset into a training set (48 tastants) and a test set (10 molecules). Between these two models, the best CART classifier used six descriptors and exhibited a moderate performance when applied to the test set.

In another two studies, Miyashita's group (Miyashita *et al.*, 1986b; Okuyama *et al.*, 1988) also used sulfamate derivatives to calibrate structure-taste relationships based on the SIMCA classifier. In the first work, 14 sweet and 36 non-sweet carbosulfamates described by molar refractivity (MR), five geometrical STERIMOL features and the Taft's σ^* descriptor were used (Miyashita *et al.*, 1986b). The SIMCA model correctly predicted 13 sweet and 24 non-sweet molecules. In addition, a set of alkyl groups were proposed as potential substituents, from which six alkylsulfamates were predicted as potential sweeteners. Among these compounds, one was synthesized and exhibited a relative sweetness of three times greater with respect to sucrose. Two years later, the same authors used 25 acyclic and 20 cyclic carbosulfamates represented by different graph theoretical invariants (Okuyama *et al.*, 1988). In addition, the acyclic sulfamates were also represented by the weighted path numbers for the rooted atom (path length from 1 to 8) and counts of self-returning walks for the rooted atom (number of steps from 2 to 13), while the atomic path numbers for the rooted atom (path length from 1 to 8) and the counts of self-returning walks for the rooted atom were also computed for cyclic sulfamates. In both cases, the SIMCA model achieved similar performance for the acyclic carbosulfamates and the cyclic derivatives.

The first *k*NN model for the discrimination between sweet and non-sweet tastants was published in 2016 (Rojas *et al.*, 2016c). A nine-descriptor *k*NN model provided the best discrimination between 433 sweet and 133 tasteless curated molecules, with similar performances for training (*NER* = 0.838) and test sets (30% of compounds), *NER* = 0.752. One year later, the same research group (Rojas *et al.*, 2017) developed an expert system that integrated unsupervised and supervised machine learning approaches. To this end, a database of 435 sweet and 214 non-sweet (bitter and tasteless) molecules were represented by means of 875 conformation-independent descriptors (Todeschini & Consonni, 2009) and extended connectivity fingerprints (ECFPs) (Rogers & Hahn, 2010), calculated by the Dragon software (Kode srl., 2018). Similarity analysis was based on the ECFPs and multidimensional scaling (MDS), while the supervised classification was carried out with the consensus predictions provided by *N*-Nearest Neighbors (N3) and partial least squares discriminant analysis (PLSDA), with good predictive accuracy on the test chemicals (*NER* = 0.848, non-assigned = 19.3%). A new consensus model was published in 2019 by Zheng (Zheng *et al.*, 2019) for a curated database of 530 sweet and 850 non-sweet molecules, which were represented by four types of ECFPs (Rogers & Hahn, 2010): 1024bit-ECFP4, 2048bit-ECFP4, 1024bit-ECFP6 and 2048bit-ECFP6. They used the *k*NN classifier, along with support vector machine (SVM), random forest (RF), gradient boosting machine (GBM) and deep neuron network (DNN) approaches to developed 1,312 individual models, as well as 96 averaged classification models. As a result, four consensus models were constructed (CM01 - CM04), and the best one (using 19 best individual models) was selected to construct the e-Sweet model. This model achieved good results in predicting the 221 test set compounds (*NER* = 0.900, *F-score* = 0.878 and *MCC* = 0.807). In a further step, a consensus regression was developed to predict the relative sweetness of 352 sweeteners.

In addition, Tuwani (Tuwani *et al.*, 2019) calibrated diverse models based on RF, ridge logistic regression and AdaBoost for the classification of sweet/non-sweet and bitter/non-bitter molecules (refer to bitter and non-bitter section). These models were named BitterSweet. For sweetness prediction, a dataset of 1,205 sweeteners and 1,171 non-sweeteners were represented by means of diverse molecular descriptors calculated in Dragon (Kode srl., 2018), Canvas (Schrödinger LLC, 2017) and ChemoPy (Cao *et al.*, 2013). The best model in terms of classification accuracy for the test set (7% of molecules) used the 2D/3D Dragon descriptors reduced by means of the Boruta algorithm and subsequently coupled with AB machine learning: *NER* = 0.834, *AUC* = 0.883 and *F-score* = 0.856.

Two years later, Fritz (Fritz *et al.*, 2021) developed the VirtualTaste prediction platform for predicting the sweet taste of molecules based on the RF classifier (VirtualSweet model). The database included 2,011 sweet and non-sweet (bitter and tasteless) molecules that were curated and standardized from the SuperSweet database (Ahmed *et al.*, 2011) and from their previous BitterSweetForest database (Banerjee & Preissner, 2018). Molecules were represented by MACCS keys (Durant *et al.*, 2002) and Morgan molecular fingerprints (Morgan, 1965; Rogers & Hahn, 2010). The RF model achieved good external prediction on the 403 test set tastants (*NER* = 0.893, *AUC* = 0.951, *F-score* = 0.888 and *ACC* = 0.893). Furthermore, the VirtualSweet model was used to virtually screen molecules from the DrugBank database and from the SuperNatural II database (Banerjee *et al.*, 2015). One year later, Yang (Yang *et al.*, 2022) used the RF and the XGBoost classifiers, along with other approaches, to calibrate diverse models for a database named Taste DB. However, this name was previously proposed by Ruddigkeit and Reymond (Ruddigkeit & Reymond, 2014). This dataset contained six families of compounds: natural (973 sweeteners and 687 non-sweeteners), artificial (402 positive and 798 negative), carbohydrate (220 sweet and 238 non-sweet), non-carbohydrate (1,155 positive and 1,476 negative), nutritive (226 sweet and 268 non-sweet) and non-nutritive (1,149 positive and 1,464 negative). For validation purposes, the datasets were divided into training and test set in a proportion of 8:2. The best artificial sweeteners model (in terms of accuracy for the test set prediction) used the RF classifier and MACCS structural keys (*NER* = 0.920 and *AUC* = 0.971), while for the carbohydrate family of compounds, the XGBoost approach and Atom pairs descriptors (*NER* = 0.926 and *AUC* = 0.974) were used. The remaining four models were developed by means of the XGBoost classifier and MOE2d descriptors with the following performances for the test set: 1) natural molecules (*NER* = 0.841 and *AUC* = 0.920); 2) non-carbohydrate compounds (*NER* = 0.867 and *AUC* = 0.947); 3) nutritive sweeteners (*NER* = 0.876 and *AUC* = 0.956); and 4) non-nutritive molecules (*NER* = 0.889 and *AUC* = 0.961). In further analysis, these authors developed regression models to predict sweetness potency (log Sw).

More recently, Bo (Bo *et al.*, 2022) developed diverse quantitative structure-taste relationships based on MLP and CNN deep learning classifiers, following the same workflow as previously described in the sweet/bitter section. In this case, the dataset contained 1,119 sweeteners and 1,101 non-sweeteners (tasteless and bitter). The best two models, in terms of their predictive ability, are the SweetMLP-Fingerprint (*NER* = 0.900, *AUC* = 0.940, *ACC* = 0.880 and *MCC* = 0.800) and SweetCNN (*NER* = 0.850, *AUC* = 0.900, *ACC* = 0.840 and *MCC* = 0.660). These models were used to predict the taste of 902 tastants of the bitter data set. Lee (Lee *et al.*, 2022) used a fully connected network (FCN), along the RF, XGB and LGBM classifiers, to propose the soft-vote ensemble approach. The curated dataset included 1,237 sweeteners and 1,054 non-sweeteners retrieved from the BitterSweet database (Tuwani *et al.*, 2019), which were represented by means of eight 2D fingerprints and diverse molecular descriptors. Among the 44 different models, the best models were LGBM applied to layered fingerprints and alvaDesc descriptors (Mauri & Bertola, 2022). These two models were used to assemble the BoostSweet model for sweetness prediction by means of the soft-vote method that averages the prediction of each model. The BoostSweet classifiers achieved good performance for the test set (211 sweeteners and 248 non-sweeteners): *NER* = 0.899, *AUC* = 0.961 and *F-score* = 0.907.

2.3. Bitter and non-bitter tastants

The prediction of sweetness has been the predominant goal for research in the computational taste framework, probably because bitterness was usually linked to toxic compounds (as described for the alkaloids). However, in the last few years, models that predict bitterness have received considerably more attention due to the use of bitterants in several applications, particularly in food and pharmaceutical industries. In contrast to the sweet/bitter models, where the main purpose was sweetness prediction, comprehensive classification models for bitterness prediction are focused on discriminating bitter from non-bitter tastants. The 14 ligand-based models found to date in the literature are summarized in Table 3.

Table 3 should be inserted around here

In 2006 Rodgers (Rodgers *et al.*, 2006) used the Naïve Bayes (NB) classifier for the bitterness prediction of small molecules. The curated dataset was composed of 649 bitterant taken from scientific literature and patents, and 13,530 hypothetical non-bitter molecules randomly selected from the MDL Drug Data Repository (MDDR). All the compounds were represented by MOLPRINT 2D circular fingerprints (aka Atom Environments) (Bender *et al.*, 2004), which were subjected to a variable subset selection. Ten years later, Huang released the first online tool, namely BitterX (Huang *et al.*, 2016), for bitterness prediction based on support vector machine (SVM) classifiers. Data of bitterants and bitterant-TAS2R interactions were retrieved from the PubMed (Sayers *et al.*, 2021) and BitterDB (Wiener *et al.*, 2012) databases. In this work, a ligand-based model and a receptor-based model were developed. In both cases, datasets were randomly split into training (80%) and test sets (20%) three times to avoid bias in the data splitting, while genetic algorithms (GAs) were used for the supervised descriptor selection. The ligand-based model was developed from a database of 539 bitterant and 539 non-bitter molecules and 46 physicochemical descriptors. The mean accuracy and the area under the curve used in the prediction of the three models were *ACC* = 0.915 and *AUC* = 0.950. On the other hand, the TAS2R receptor recognition model used 260 bitterants and 260 non-bitter molecules (negative), and 20 physicochemical and 15 receptor descriptors with slightly lower prediction quality (*ACC* = 0.798 and *AUC* = 0.823).

RF classifiers were also used for bitterness prediction (Fritz *et al.*, 2021; Tuwani *et al.*, 2019). Tuwani published the BitterSweet model (Tuwani *et al.*, 2019) for the classification of bitterants, in which they followed the same workflow as presented in the sweet/non-sweet section. The RF classifier, coupled with PCA reduction of ChemoPy descriptors, achieved a higher non-error rate in prediction for the test set (154 molecules): *NER* = 0.819, *AUC* = 0.880 and *F-score* = 0.838. This was then used to predict the taste of external molecules available in the FlavorDB, FooDB, SuperSweet (Ahmed *et al.*, 2011), Super Natural II (Banerjee *et al.*, 2015), DSSTox (Richard & Williams, 2002) and DrugBank libraries. In a further analysis, molecular taste of Bitter new, UNIMI set and Phytochemical dictionary databases (Dagan-Wiener *et al.*, 2017) were also predicted. Fritz (Fritz *et al.*, 2021) implemented the VirtualBitter model following the same workflow as for the sweetness prediction (refer to the sweet and non-sweet section). They retrieved molecules from the BitterDB (Dagan-Wiener *et al.*, 2019) and from their BitterSweetForest model (Banerjee & Preissner, 2018), in order to model 1,612 bitterants and non-bitter (sweet and tasteless) molecules. The RF classifier exhibited acceptable performances in prediction (20% test compounds): *NER* = 0.898, *AUC* = 0.956, *F-score* = 0.882 and *ACC* = 0.901. In addition, when a molecule is predicted as bitterant, the webserver provides the potential bitter target prediction for the 25 human bitter receptors (hTAS2Rs) based on a similarity-based analysis. Finally, the VirtualBitter model was used to virtually screen diverse molecules from the DrugBank database and the SuperNatural II database (Banerjee *et al.*, 2015).

Between 2020 and 2021, Charoenkwan's group published three webservers for taste prediction of a curated database of 320 bitter peptides and 320 non-bitter peptides (BTP640), randomly generated from BIOPEP (Minkiewicz *et al.*, 2008). The dataset was split into a training set and a test set (80:20). NB and RF classifiers as well as several other classifiers were used: *k*NN, scoring card method (SCM), bidirectional encoder representation from transformers (BERT), support vector machine (SVM), decision tree (DT), extremely randomized trees (ETree), linear support vector classifier (SVC), logistic regression (LR), multi-layer perceptron (MLP) and extreme gradient boosting (XGB). The SCM classifier (Huang *et al.*, 2012), which was used through the dipeptide propensity score (PDS) and optimized with GAs, achieved good results in prediction (*ACC* = 0.844, *AUC* = 0.904 and *MCC* = 0.688) when compared to the SVM, RF, NB, *k*NN and DT, and it was included in the iBitter-SCM webserver application (Charoenkwan *et al.*, 2020a). The authors stated that iBitter-SCM constituted a useful tool for the high-throughput prediction and *de novo* design of novel bitterant peptides. Another webserver, named BERT4Bitter (Charoenkwan *et al.*, 2021a), automatically generates feature descriptors for peptides through the BERT algorithm. This model achieved the best test set performance (*ACC* = 0.922, *AUC* = 0.964 and *MCC* = 0.844) with respect to the other calibrated classifiers (DT, ETree, *k*NN, SVC, LR, MLP, NB, RF, SVM and XGB). For the webserver iBitter-Fuse (Charoenkwan *et al.*, 2021b), five groups of molecular features were calculated: 20 amino acid composition (AAC), 400 dipeptide composition (DPC), 21 pseudo amino acid composition (PAAC), 22 amphiphilic pseudo amino acid composition (APAAC), 531 physicochemical properties from AAindex (AAI), as well as a new group achieved by fusing features (994 descriptors). Ten SVM models were calculated, providing excellent prediction quality (*ACC* = 0.930, *AUC* = 0.933 and *MCC* = 0.859). As described in their previous work, the authors calibrated other machine learning models and demonstrated that the iBitter-Fuse model was superior in any case (refer to Table 3 for the comparison between the iBitter-Fuse and the iBitter-SCM and BERT4Bitter classifiers).

Dagan-Wiener used the Adaptive Boosting (AdaBoost) classifier for the first time in this framework to create the BitterPredict model (Dagan-Wiener *et al.*, 2017). The dataset was composed of 691 bitterants (632 from the BitterDB (Wiener *et al.*, 2012)) and 1,917 non-bitter compounds retrieved from several sources, which included 1,360 non-bitter flavors, 336 sweeteners, 186 tasteless molecules and 35 molecules labelled as non-bitter (molecules not described by the word bitter in the source). Each compound was represented by 59 molecular descriptors. The model was finally trained with 16 molecular descriptors and demonstrated predictive ability for the test set (30% of molecules) with *NER* = 0.812 and *ACC* = 0.832. Subsequently, the bitter class was evaluated for three external datasets, namely Bitter New (*Sn* = 0.739), UNIMI set (*Sn* = 0.783) and Phytochemical Dictionary (Baxter *et al.*, 1999) (*Sn* = 0.980 and *Sp* = 0.692). In a further step, the BitterPredict classifier was applied to achieve prospective predictions of compounds from the FooDB, DrugBank, ChEBI and the database of natural products. One year later, Zheng (Zheng *et al.*, 2018) developed several models based on the gradient boosting machine (GBM), as well as *k*NN, SVM, RF and two deep neuron networks (DNN2 and DNN3). These authors used a curated dataset of 707 bitterants and 592 non-bitter compounds (132 tasteless, 17 non-bitter and 443 sweet). Molecules were represented by means of several extended connectivity fingerprints (ECFPs): 1024bit-ECFP4, 2048bit-ECFP4, 1024bit-ECFP6 and 2048bit-ECFP6. In order to avoid bias due to partition, the splitting of the dataset was repeated 19 times for the *k*NN, SVM, GBM and RF models, and three times for the DNN2 and DNN3 models. Thus, 1,312 individual models and 96 average models were calibrated and consensus voting was used to obtain nine models (CM01 - CM09), which were integrated in the server e-Bitter tool. The best model (CM01) exhibited the following parameters for the test set (20% of compounds): *F-score* = 0.936, *ACC* = 0.929 and *MCC* = 0.856.

The XGBoost classifier was also used for bitterness prediction. Margulis proposed the BitterIntense model (Margulis *et al.*, 2021) for the classification of bitter molecules into very bitter and non-very bitter (including non-bitter) classes. A dataset of 721 compounds were obtained from behavioral studies using the rat brief access taste aversion (BATA), BitterDB (Dagan-Wiener *et al.*, 2019), Analyticon repository of natural compounds on Kaggle, as well as from their previous dataset BitterPredict (Dagan-Wiener *et al.*, 2017). Subsequently, 3D structures were used to calculate Canvas molecular descriptors (Schrödinger LLC, 2017) and QikProp features (ADME descriptors) (Schrödinger LLC, 2015). The XGBoost model achieved acceptable prediction on the test set (105 tastants): *NER* = 0.790, *F-score* = 0.700 and *ACC* = 0.800. Moreover, the BitterIntense model was used for analyzing the connection between toxicity and the level of bitterness of molecules, as well as for potential repurposing of COVID-19 targets. Independently, Bai developed the Children's Bitter Drug Prediction System' (CBDPS) (Bai *et al.*, 2021) for the bitterness prediction of medicines. The experimental dataset was retrieved from published works and the BitterDB (Dagan-Wiener *et al.*, 2019), which consisted of 1,732 tastants with a balanced number between bitter and non-bitter tastants (ratio of 1:1). Then, 166 MACCS structural keys and 114 ChemoPy descriptors (Cao *et al.*, 2013) were used to calibrate four models based on the XGBoost and RF classifiers. Among these models, the optimal one was obtained with the XGBoost classifier and the MACCS structural keys, and achieved the following performance in cross-validation: *F-score* = 0.881 and *ACC* = 0.882. In a last step, the CBDPS model was applied to the screening of the external dataset of 222 children's oral medicines.

The XGBoost classifier was also applied to develop the BitterMatch model (Margulis *et al.*, 2022). A curated dataset of 303 bitterants resulted in 4,501 pairs of ligand-receptor associations (740 positives and 3,761 negatives). Optimized bitterants were used to calculate Canvas descriptors (Schrödinger LLC, 2017), while 3 sets of features were computed for receptors. The BitterMatch algorithm was divided into two scenarios: *filling the gaps* and *new ligands*. In both cases, 20% of the molecules were considered as test sets, keeping in mind the proportion of the classes (repeated 100 times). In *filling the gaps,* the best model included chemical properties and neighbor-informed chemical similarity features with an average recall-precision of 0.759. In contrast, the *new ligands* scenario considered only chemical properties of ligands and receptors, as well as neighbors-informed ligand similarity features (average recall-precision of 0.699). Afterwards, it was used to predict associations for 12 external bitterants and drugs from the DrugBank.

More recently, Bo (Bo *et al.*, 2022) calibrated quantitative structure-taste relationships based on MLP and CNN deep learning classifiers (as described before in the sweet/bitter and sweet/non-sweet sections). In this work, a dataset of 797 bitterants and 1,436 non-bitterants (sweet and tasteless) was used. The BitterMLP-Descriptor classifier with seven RDKit descriptors exhibited similar validation performance (*NER* = 0.820, *AUC* = 0.940, *ACC* = 0.840 and *MCC* = 0.660) with respect to the BitterCNN classifier (*NER* = 0.790, *AUC* = 0.880, *ACC* = 0.810 and *MCC* = 0.600). As described in the sweet/non-sweet models, these two classifiers were used to analyze 1,229 tastants from the sweet data set. De León (De León *et al.*, 2022) calibrated SVM, RF, AdaBoost and *k*NN models for a curated dataset of 932 bitterants and 1,908 non-bitter molecules retrieved from BitterDB (Dagan-Wiener *et al.*, 2019), Fenaroli's Handbook of flavours (Burdock, 2010) and the dataset of Rojas (Rojas *et al.*, 2016c). The compounds were represented by ECFPs and 22 selected Mordred descriptors (Moriwaki *et al.*, 2018) on the basis of their probability density. For validation purposes, 20% of the molecules were included in the test set. The two best classifiers turned out to be SVM (ACC_{train} = 0.836 and ACC_{test} = 0.870) and AdaBoost (ACC_{train} = 0.842 and ACC_{test} = 0.847) based on ECFPs and descriptors, respectively. In addition, the UNIMI dataset (Dagan-Wiener *et al.*, 2017) was used as the external set to validate the performance of Premexotac models.

2.4. Umami and non-umami tastants

There are fewer ligand-based (LB) machine learning models that have been developed for the discrimination between umami and non-umami peptides. This could be due to the higher complexity of sensory evaluation and related costs than those related to the evaluation of sweet and bitter molecules.

For the first model, named iUmami-SCM (Charoenkwan *et al.*, 2020b), the experimental information for umami peptides was retrieved from the literature and from the BIOPEP-UWM database, while bitter peptides, previously studied by the authors, were considered as non-umami molecules. The UMP442 database (140 umami and 302 non-umami peptides) was used to calibrate a SCM classifier based on a dipeptide propensity score (PDS), as described in the iBitter-SCM model (Charoenkwan *et al.*, 2020a). The best model achieved good results in prediction (20% of test molecules): *AUC* = 0.898, *ACC* = 0.865, *MCC* = 0.679, *Sn* = 0.714 and *Sp* = 0.934. In addition, the model's performance was compared with six ML classifiers (SVM, RF, MLP, NB, *k*NN and DT). In the second application, the same group of Charoenkwan combined six well-known ML classifiers (ETree, *k*NN, LR, PLS, RF and SVM) in the UMPred-FRL model (Charoenkwan *et al.*, 2021c). To this end, they used molecules of the UMP442 database (Charoenkwan *et al.*, 2020b), which were represented by seven feature descriptors: amino acid composition (AAC), amphiphilic pseudo-amino acid composition (APAAC), dipeptide composition (DPC), composition (CTDC), transition (CTDT), distribution (CTDD) and pseudo-amino acid composition (PAAC). The UMPred-FRL predictor was assembled by the best 7 informative features (SVM-AAC, PLS-AAC, SVM-CTDC, RF-DPC, RF-CTDC, PLS-APAAC and LRDPC), and exhibited better performances when compared to the iUmami-SCM classifier prediction (*AUC* = 0.919, *ACC* = 0.888 and *MCC* = 0.735).

In 2022, Pallante developed the Virtuous Umami platform (Pallante *et al.*, 2022) for umami prediction based on SVM classifiers and the Charoenkwan's UMP442 database (Charoenkwan *et al.*, 2020b). Due to the unbalanced classes, umami peptides were randomly duplicated to balance the class cardinalities. Subsequently, 1,613 conformation-independent Mordred features (Moriwaki *et al.*, 2018) were subjected to feature selection by means of different approaches, which were used to calibrate diverse SVM models. The best prediction was achieved by consensus between two models (12 features), which exhibited a slightly lower performance in prediction (*AUC* = 0.850, *F-score* = 0.793 and *ACC* = 0.876) when compared to the iUmami-SCM and UMPred-FRL predictors. The effectiveness of the model was visually shown by means of t-SNE. Finally, the umami predictor was used to virtually screen the FooDB, FlavorDB, PhenolExplorer, Natural Product Atlas and PhytoHub databases.

Recently, Dutta proposed the identification of optimal sequential residue patterns for umami and bitter peptides (Dutta *et al.*, 2022a). These authors used a curated database of 292 bitter and 146 umami compounds retrieved from Charoenkwan's UMP442 database (Charoenkwan *et al.*, 2020b) and others sources. Each peptide was represented by the following coarse-grained representation: hydrophobic (H), polar and hydrophilic (P), positively charged (+) and negatively charged (−). Afterwards, seven libraries of peptides were created by repeating a fixed set of coarse-grained patterns. To select the best length, the dataset of taste-labeled peptides was split into a training set (80%) and a test set (20%) by means of stratified random sampling. A length of five (N = 5) was selected as the best coarse-grained pattern, where bitter peptides were represented by one hydrophobic followed by four polar residues (HPPPP), while umami peptides had two negative followed by three polar residues (−−PPP). In a further step, the authors tested this method by using two bitter proteins (Patatin-T5 and Legumin-A), where 8 and 5 peptide sequences with the aforementioned course-grain pattern were identified. This approach allowed the rapid screening and identification of sequential information patterns hidden in long chain peptides and proteins, rather than predicting the taste class of peptides (no classification performances were reported).

2.5 Bitter, sweet and umami tastant

Dutta developed the first deep learning classifier to discriminate among sweet, bitter and umami tastants (Dutta *et al.*, 2022b). The curated dataset was composed of 1,938 bitterants, 2,079 sweeteners and 98 umami compounds, which were retrieved from the ChemTastesDB database (Rojas *et al.*, 2022) and the BitterSweet dataset (Tuwani *et al.*, 2019). Afterwards, 102 RDKit molecular descriptors were used after a filtering process. For pattern recognition, the authors developed two chemical spaces based on PCA and t-SNE, along with a functional group analysis by computing the frequency of predefined fragments. Then, a deep neural network (DNN) with two hidden layers of 100 neurons was trained with 200 epochs. For balancing the cardinality of the umami class, the synthetic minority oversampling technique (SMOTE) for data augmentation was used. The DNN model was interpreted by means of the Shapley additive explanations (SHAP). The DNN model achieved good predictive performance (15% of compounds): NER = 0.901 and ACC = 0.887. Moreover, a graph neural network (GNN) was also tested with a slightly lower quality on external prediction (NER = 0.865 and ACC = 0.896). Independently, Xiu (Xiu *et al.*, 2022) used the BitterSweet dataset (Tuwani *et al.*, 2019) to develop the PyUmami model, which combined sweet and bitter classifiers based on multilayer perception (MLP) and Mordred descriptors. Then, the sweet-MLP (ACC = 0.830 and AUC = 0.897) and bitter-MLP models (ACC = 0.81 and AUC = 0.895) were used to predict the sweetness of 1,040 bitterants from the BitterDB, and the bitterness of 14,175 sweeteners from the SWEET-DB, respectively. Only 169 tastants predicted as both sweet/bitter by the PyUmami model were submitted to docking analysis with the T1R2/T1R3 and hT2R1 receptors.

Finally, 18 targets were experimentally verified for sweet, bitter and umami intensities by means of electronic tongue analysis, and only 8 tastants were predicted to be non-toxic by means of twelve QSAR approaches and three virtual Adverse Outcome Pathway (vAOP) models.

2.6. Sour and non-sour tastants

Only one LB classifier for the discrimination between sour and non-sour compounds has been proposed (Fritz *et al.*, 2021). Information of molecules was retrieved from ChEMBL (Gaulton *et al.*, 2012) and curated from the PubMed database (Sayers *et al.*, 2021). The dataset consisted of 1,347 compounds divided into a training set and a test set of 1,214 and 133 molecules, respectively. The model, named VirtualSour, was a ligand-based approach considering the RF classifier integrated with the augmented random data sampling method. The model achieved good results in cross-validation (*NER* = 0.955, *AUC* = 0.998, *F-score* = 0.980 and *ACC* = 0.978,) and prediction (*NER* = 0.896, *AUC* = 0.994, *F-score* = 0.842 and *ACC* = 0.977).

2.7 General trends in taste modelling

When looking at the evolution of modelling approaches for predicting the different tastes, common trends and tendencies can be seen. Figure 3 shows the number of molecules (included in both training and test set) used for the development of structure-property models as a function of the publication year, starting from the very beginning of the modelling era (1980) up to 2022. First of all, it is apparent that the number of chemicals used to train or test QSAR models has greatly increased (note that the y axis of Figure 3 is in log10 units). While the first modeling attempts considered a few dozen chemicals, the number increased to several hundreds from 2000 to 2010. In addition, models were initially developed considering only small families of compounds (for instance aldoximes, perillartines, aspartyl dipeptides and sulfamates), which established restricted chemical spaces for only these types of compounds. The most relevant increase in the number of chemicals occurred after 2015, when scientists started to use several thousand molecules to develop new models for taste prediction. Interestingly, the study for bitter prediction published by Rodgers in 2006 (Rodgers *et al.*, 2006) used 13,530 molecules randomly selected from the MDL Drug Data Repository under the assumption that this was representative of the bitterness chemical space. However, these molecules were not validated with experimental sensory data as considered in the most recently published works.

Figure 3 should be inserted around here

The large growth of the number of molecules used in the development of models that started in 2015 is probably due to several research groups who concentrated their efforts on creating more extensive and comprehensive databases, such as SuperSweet (Ahmed *et al.*, 2011), BitterDB (Wiener *et al.*, 2012), ChEMBL (Gaulton *et al.*, 2012) and Super Natural II (Banerjee *et al.*, 2015). These databases collected and cataloged a greater number of substances associated with their molecular structures and experimental taste values, which enabled the subsequent development of models based on a significantly higher number of chemicals in the years after 2015. These large databases included heterogeneous molecules, which allowed the extension of chemical spaces and, in fact, some attempts were made for virtual screening of potential new tastants in several available databases, which were complemented, in some cases, with docking analysis and experimental sensory evaluation of the elicited tastants.

Another general trend is related to the type of analyzed taste. Figure 3, shows that in the first 29 years from the first model developed in 1980, sweetness was the principal interest. Within this modelling framework, only models for the discrimination of sweet chemicals versus bitter or non-sweet molecules were taken into account. Afterwards, due to the development of more comprehensive databases, models for the prediction of bitterness were proposed in addition to sweetness. The interest in bitterness prediction could be related to the increasing interest of using bitterants as food and pharmaceutical additives along with other applications. Starting from 2020, umami prediction proved to be another attractive topic in the scientific community. The increasing interest in modelling this taste is mainly related to Asian research groups, due to the importance of umami in oriental gastronomy. On the other hand, modelling of sourness and saltiness is limited by the reduced number of molecules that imprint these tastes.

The increasing number of molecules used to model tastants also enabled a better estimation of predictive performance; that is, the accuracy in the prediction of the taste of chemicals which were not used for model training. Validation is fundamental in the development of QSARs and usually consists of the use of some chemicals, with known experimental taste values but not involved in the model training, as the test molecules. The first studies did not generally account for model validation. Until 2016 less than 10 chemicals were used in a couple of studies to validate models for discrimination between sweet and bitter tastants (Table 1), while for the classification of sweet and non-sweet chemicals, no test compounds were considered until 2005 and just a few in the studies published between 2006 and 2009 (Table 2). On the other hand, the number of substances used for model validation has grown enormously in recent years and now, hundreds of molecules are normally used for validation purposes.

Finally, the increasing availability of newly synthesized chemicals has influenced the type of machine learning approaches that have been used to establish molecular structure-taste relationships. Initially only simple classification algorithms were used (such as Discriminant Analysis and CART), whereas in the last decade, advanced approaches have been frequently applied, such as RF, SVM, boosting algorithms and Neural Networks. This is a general trend in the framework of machine learning, which has been supported by the computational and technological advancements of the latest decades. However, unlike traditional approaches, the newer and novel classification methods require a tuning phase for the selection of optimal values of their hyperparameters. This tuning phase is executed by optimizing the models on a further set of chemicals, usually named an evaluation set, which has to be added to the training set (used for the learning phase) and the test set (used for the final validation phase). Therefore, execution of the tuning phase requires a more extended number of chemicals for their calculation.

It is interesting to note that although a very limited number of descriptors was used in the first developed models, the evolution of modeling approaches has not caused a considerable increase in the complexity of the models. In many cases the total number of descriptors used for the development of models is measured in the 10s, and only a few hundred descriptors have been used in some models for the discrimination of sweet and non-sweet tastants. Of course, molecular fingerprints are a special case, since the thousands of binary bits they include have to be considered simultaneously as a holistic description of the molecular structure. As in other modelling frameworks, the limited number of descriptors is probably due to the maintenance of a correct balance between the model complexity, predictive ability and interpretability.

In earlier models for sweet prediction, descriptors mainly related to molecular size and bulkiness were used while recently, quantum-chemical descriptors were considered as well as different types of fingerprints and descriptors calculated by means of different software including Dragon, RDKit, Mordred, Pybel, alvaDesc and MOE2d. From an analysis of the most frequent molecular descriptors in models for bitterness, the relevant structural features are the presence of carbon/oxygen groups, sugar moieties, quaternary carbon centers and highly branched carbon centers, physicochemical properties, specific properties of the molecular surface and hydrophobicity. More specifically, the bitterness of peptides is strongly related to composition of amino acids, dipeptides and pseudo amino acids. Finally, molecular descriptors used for modelling umami taste are mainly linked to the presence of hydrophilic amino acids with negative charge and low molecular weights. In addition, patterns in the scaffolds related to amino acid composition; specifically glutamic acid (Glu) and aspartic acid (Asp) amino acid, were found to be crucial for umami prediction of peptides.

3. Conclusions

In this paper, we present a logical, comprehensive and critical review of the current state of ligand-based models of quantitative structure-property relationships along with the history of the prediction of the taste of molecules. Models detailed here complement previously published reviews available in the literature. Although the main modeling applications presented in this review relate to the prediction of molecular sweetness and bitterness, there is a notable increase in the interest and proposed application of QSAR models for the prediction of umami and sour tastants. It is notable that many authors cited in this review attempted to use the largest possible databases of tastants, as well as to improve the chemical representation of these databases through the use of several molecular descriptors, structural keys and fingerprints. In addition, this review reflects the wide variety of machine learning approaches used by investigators in order to calibrate more general models used in the prediction of properties of new molecules. In the future, it is expected that *in silico* methods will increase the application of predictive models in food chemistry (foodinformatics) in order to better understand the mechanisms involved in taste prediction. In addition, predictive models may provide useful tools to discover new molecular tastants with potential uses as raw-materials or additives in the food and pharmaceutical industries. Finally, our recommendation to chemists involve in taste prediction is to develop the largest possible molecular tastant databases to be used with novel classifiers in order to develop models able to predict more than two classes at a time. This expanded capability will greatly advance the science of foodinformatics.

4. Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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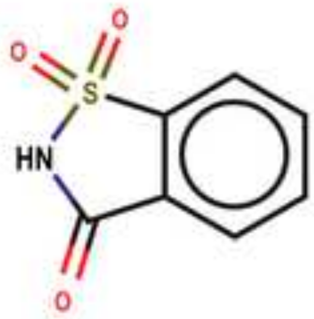
Figure 1. Taste changes of saccharin when introducing the nitro and amino molecular fragments in diverse position of the chemical scaffold.

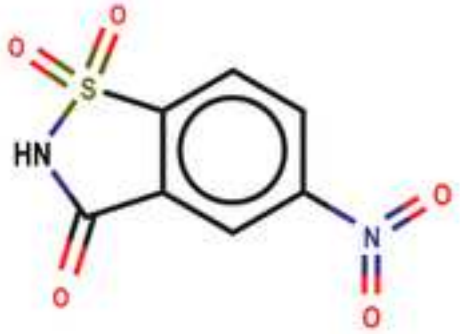
Figure 2. Representation of classification boundaries (black lines) between sweet (blue) and bitter (red) chemicals in the space of the first two t-SNE dimensions (latent variables for PLSDA). The results are presented for different classifiers.

Figure 3. Number of molecules (expressed as log10) used for the calculation of models for taste prediction vs publication year.

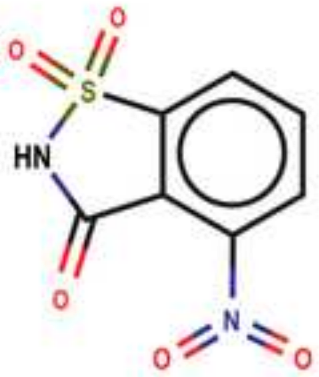
Figure 1



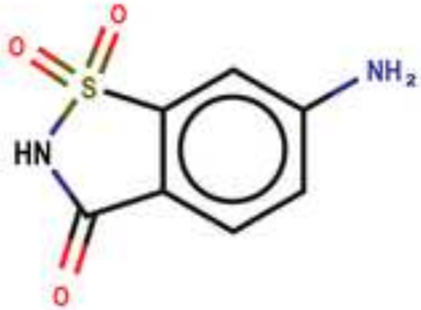
Saccharin (sweet)



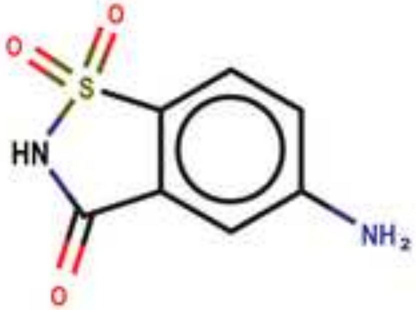
5-Nitrosaccharin (Bitter)



p-Nitrosaccharin (Sweet/Bitter)



6-Aminosaccharin (Sweet/Tasteless)



5-Aminosaccharin (Tasteless)

Figure 2

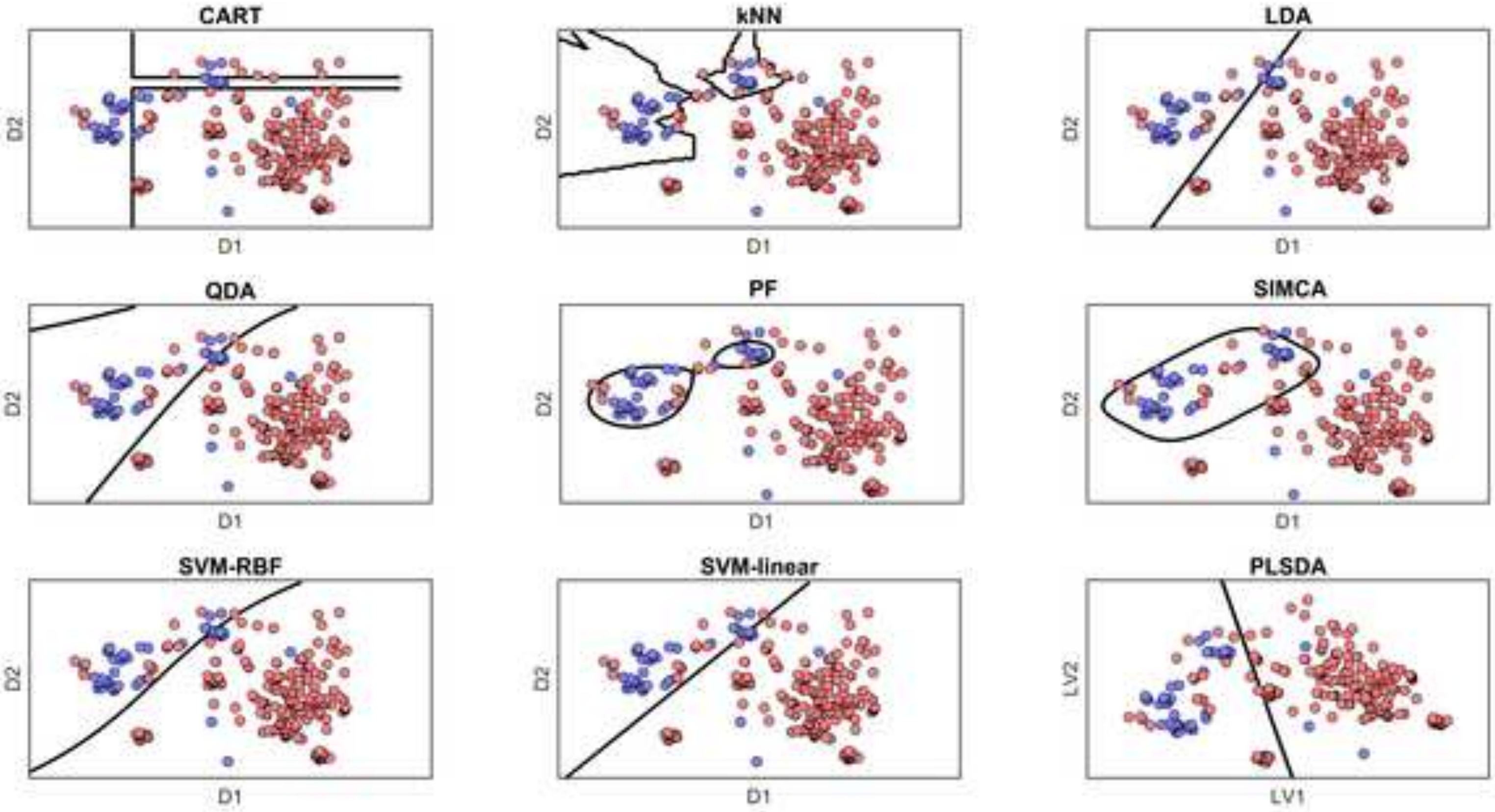
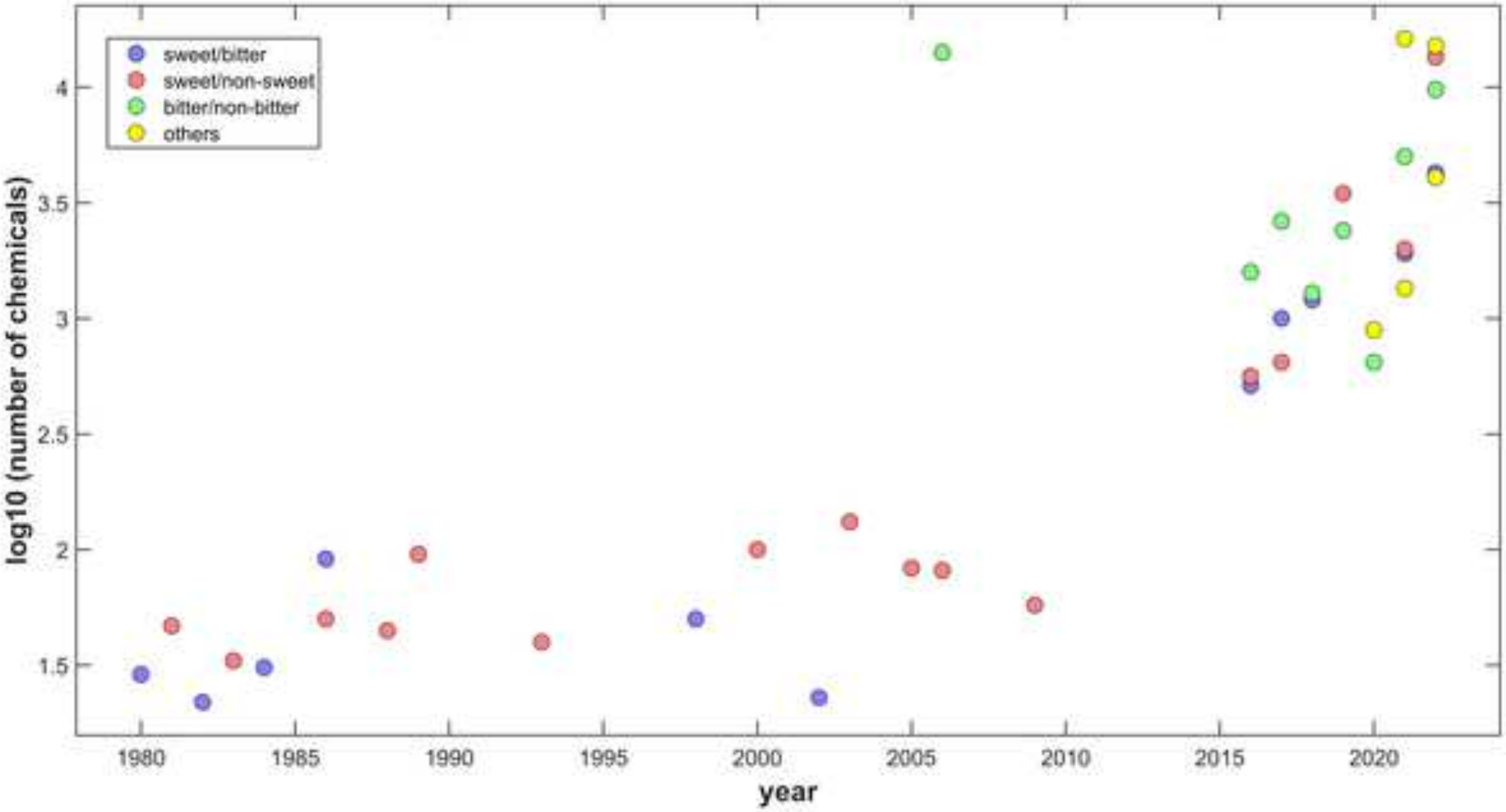

CART
kNN
LDA
QDA
PF
SIMCA
SVM-RBF
SVM-linear
PLSDA
D1
D2
LV1
LV2

Figure 3



sweet/bitter
sweet/non-sweet
bitter/non-bitter
others
log10 (number of chemicals)
4
3.5
3
2.5
2
1.5
1980
1985
1990
1995
2000
2005
2010
2015
2020
year

Table 1. Classification-based machine learning models for the discrimination between sweet and bitter tastants. *d* is the number of descriptors, *n* is the number of molecules.

Table 2. Classification-based machine learning models for the discrimination between sweet and non-sweet tastants. *d* is the number of descriptors, *n* is the number of molecules.

Table 3. Classification-based machine learning models for the prediction of bitterness. *d* is the number of descriptors, *n* is the number of molecules.

Table 1

reference	URL	Model name	Classifier	*d*	*training*				*test*			
					n	*NER*	*AUC*	*F-score*	*n*	*NER*	*AUC*	*F-score*
(Kier, 1980)	--	--	LDA	2	20	0.850	--	--	9	0.875	--	--
(Takahashi *et al.*, 1982)	--	--	*k*NN	3	22	0.909	--	--	--	--	--	--
			LDA			1	--	--	--	--	--	--
(Takahashi *et al.*, 1984)	--	--	LDA	3	22	1	--	--	9	0.775	--	--
				2		0.955	--	--		0.775	--	--
(Miyashita *et al.*, 1986a)	--	--	SIMCA	5	91	0.840			--	--	--	--
(Drew *et al.*, 1998)	--	--	DA	11	50	1	--	--	--	--	--	--
(Spillane *et al.*, 2002)	--	--	Biplot	2	23	0.862	--	--	--	--	--	--
			LDA	4		0.850	--	--	--	--	--	--
			QDA	4		0.900	--	--	--	--	--	--
(Rojas *et al.*, 2016c)	--	--	*k*NN	4	356	0.864	--	--	152	0.789	--	--
(Chéron *et al.*, 2017)	http://sebfiorucci.free.fr/SweetenersDB/	--	RF	5^a	796	0.997	--	--	200	0.914	--	--
(Banerjee & Preissner, 2018)	--	BitterSweetForest	RF	2,048	961	0.950^b	0.980	0.940	241	0.967^b	0.980	0.920
(Goel *et al.*, 2021)	--	--	RF	8	1,537	0.908	--	--	385	0.855	--	--
(Bo *et al.*, 2022)	--	BitterSweetMLP-Fingerprint	MLP	17	1,637	0.870	0.950	--	409	0.880	0.950	--
(Maroni *et al.*, 2022)	https://github.com/gabribg88/VirtuousSweetBitter https://virtuoush2020.com/	--	GBM	9	2,195	0.893	0.950	0.883	--	--	--	--

[a] number of descriptors for the tree depth; [b] calculated as Accuracy (*ACC*)

Table 2

reference	URL	Model name	Classifier	*d*	*training*				*test*			
					n	*NER*	*AUC*	*F-score*	*n*	*NER*	*AUC*	*F-score*
(Spillane & McGlinchey, 1981)	--	--	DA-plot	2	47	0.957[b]	--	--	--	--	--	--
(Spillane *et al.*, 1983)	--	--	LDA	3	33	0.807	--	--	--	--	--	--
(Miyashita *et al.*, 1986b)	--	--	SIMCA	4	50	0.798	--	--	--	--	--	--
(Okuyama *et al.*, 1988)	--	--	SIMCA	1[a]	25	0.868	--	--	--	--	--	--
					20	0.808	--	--	--	--	--	--
(Spillane & Sheahan, 1989)	--	--	DA-plot	2	17	0.824[b]	--	--	--	--	--	--
			LDA	3	23	0.642	--	--	--	--	--	--
					56	0.773	--	--	--	--	--	--
(Spillane *et al.*, 1993)	--	--	DA-plot	2	40	--	--	--	--	--	--	--
(Spillane *et al.*, 2000)	--	--	QDA	4	101	0.801	--	--	--	--	--	--
(Spillane *et al.*, 2003)	--	--	CART	4	132	0.815	--	--	--	--	--	--
(Kelly *et al.*, 2005)	--	--	CART	6	75	0.768	--	--	8	0.750	--	--
(Spillane *et al.*, 2006)	--	--	CART	7	70	0.807	--	--	12	0.909	--	--
(Spillane *et al.*, 2009)	--	--	CART	6	48	0.950	--	--	10	0.625	--	--
(Rojas *et al.*, 2016c)	--	--	*k*NN	9	396	0.838	--	--	170	0.752	--	--
(Rojas *et al.*, 2017)	--	--	Expert System	--	488	0.892	--	--	161	0.848	--	--
(Zheng *et al.*, 2019)	https://www.dropbox.com/sh/1fmlv7nf6wofgcp/AADBJzFbbbiNRJUP0806wSyna?dl=0	e-Sweet	Consensus	--	883	0.870	--	0.850	221	0.900	--	0.878
(Tuwani *et al.*, 2019)	https://github.com/cosylabiiit/bittersweet/ https://cosylab.iiitd.edu.in/bittersweet/	BitterSweet	AdaBoost	--	2,205	0.856	0.918	0.858	161	0.834	0.883	0.856
(Fritz *et al.*, 2021)	http://virtualtaste.charite.de/VirtualTaste/	VirtualSweet	RF	--	1,608	0.970	0.990	0.870	403	0.893	0.951	0.888
(Yang *et al.*, 2022)		--	RF	241	959	0.873	0.958	--	241	0.920	0.971	--

	https://github.com/ifyoungnet/ChemSweet		XGBoost	95	366	0.905	0.956	--	92	0.926	0.974	--
				105	1,327	0.834	0.926	--	333	0.841	0.920	--
				124	2,104	0.870	0.947	--	527	0.867	0.947	--
				102	394	0.893	0.937	--	100	0.876	0.956	--
				122	2,091	0.875	0.949	--	522	0.889	0.961	
(Bo *et al.*, 2022)	--	SweetMLP-Fingerprint	MLP	--	1,776	0.860	0.930	--	444	0.900	0.940	--
		SweetCNN	CNN			0.860	0.900	--		0.850	0.900	--
(Lee *et al.*, 2022)	--	BoostSweet	Soft-vote consensus	--	1,832	--	--	--	459	0.899	0.961	0.907

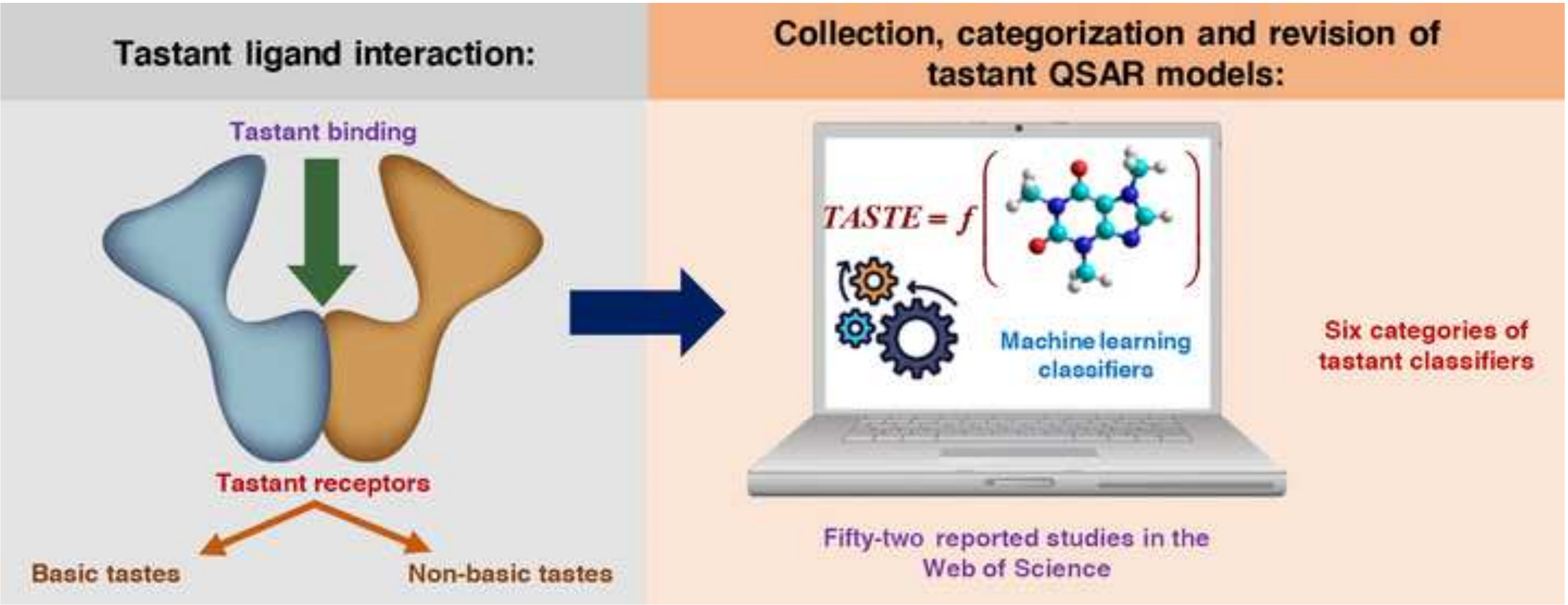
[a] number of principal components (PCs); [b] calculated as Accuracy (*ACC*)

Table 3

reference	URL	Model name	Classifier	*d*	*training*				*test*			
					n	*NER*	*AUC*	*F-score*	*n*	*NER*	*AUC*	*F-score*
(Rodgers *et al.*, 2006)	--	--	Naïve Bayes	10	14,179	0.805	--	--	--	--	--	--
(Huang *et al.*, 2016)	http://mdl.shsmu.edu.cn/BitterX	BitterX	SVM	46	862	0.879[b]	--	--	216	0.915[b]	0.950	--
				35	416	0.767[b]	--	--	104	0.798[b]	0.823	--
(Dagan-Wiener *et al.*, 2017)	https://github.com/Niv-Lab/BitterPredict1	BitterPredict	AdaBoost	16[a]	1,827	0.921	--	--	781	0.812	--	--
(Zheng *et al.*, 2018)	https://www.dropbox.com/sh/3sebvza3qzmazda/AADgpCRXJtHAJzS8DK_P-q0ka?dl=0	e-Bitter	Consensus	--	1,040	--	--	--	259	0.929[b]	--	0.936
(Tuwani *et al.*, 2019)	https://github.com/cosylabiiit/bittersweet/ https://cosylab.iiitd.edu.in/bittersweet/	BitterSweet	RF	--	2,257	0.754	0.852	0.698	154	0.819	0.880	0.838

(Charoenkwan *et al.*, 2020a)	http://camt.pythonanywhere.com/	iBitter-SCM	SCM	--	512	0.871[b]			128	0.844[b]		
(Margulis *et al.*, 2021)	--	BitterIntense	XGBoost	8	616	0.870[b]	--	0.820	105	0.790	--	0.700
(Charoenkwan *et al.*, 2021a)	http://pmlab.pythonanywhere.com/BERT4Bitter	BERT4Bitter	BERT	--	512	0.861[b]	0.915	--	128	0.922[b]	0.964	--
(Fritz *et al.*, 2021)	http://virtualtaste.charite.de/VirtualTaste/	VirtualBitter	RF	--	1,289	0.960	0.975	0.946	323	0.898	0.956	0.882
(Charoenkwan *et al.*, 2021b)	http://camt.pythonanywhere.com/iBitter-Fuse	iBitter-Fuse	SVM	36	512	0.918[b]	0.937	--	128	0.930[b]	0.933	--
(Bai *et al.*, 2021)	--	CBDPS	XGBoost	--	1,296	0.882[b]	--	0.881	112	--	--	--
(Bo *et al.*, 2022)	--	BitterMLP-Descriptor	MLP	15	1,787	0.830	0.920	--	446	0.820	0.940	--
		BitterCNN	CNN	--		0.770	0.870	--		0.790	0.880	--
(Margulis *et al.*, 2022)	https://github.com/YuliSl/BitterMatch	BitterMatch	XGBoost	20	3,601	0.759[c]	--	--	900	--	--	--
					242	0.699[c]	--	--	61	--	--	--
(De León *et al.*, 2022)	--	Premexotac	SVM	512	2,272	0.836[b]	--	--	568	0.870[b]	--	--
			AdaBoost	18		0.842[b]	--	--		0.847[b]	--	--

[a] descriptors with the most significant contribution; [b] calculated as Accuracy (*ACC*), [c] reported as recall-precision


Tastant ligand interaction:
Tastant binding
Tastant receptors
Basic tastes
Non-basic tastes
Collection, categorization and revision of tastant QSAR models:
TASTE = f
Machine learning classifiers
Six categories of tastant classifiers
Fifty-two reported studies in the Web of Science