Review

Research and development of taste sensors as a novel analytical tool

By Kiyoshi Toko[*1,†]

(Edited by Toshio Yanagida, m.j.a.)

Abstract: Gustatory and olfactory receptors receive multiple chemical substances of different types simultaneously, but they can barely discriminate one chemical species from others. In this article, we describe a device used to measure taste, *i.e.*, taste sensors. Toko and colleagues developed a taste sensor equipped with multiarray electrodes using a lipid/polymer membrane as the transducer in 1989. This sensor has a concept of global selectivity to decompose the characteristics of a chemical substance into taste qualities and to quantify them. The use of taste sensors has spread around the world. More than 600 examples of taste-sensing system have been used, while providing the first "taste scale" in the world. This article explains the principle of taste sensors and their application to foods and medicines, and also a novel type of taste sensor using allostery. Taste-sensor technology, the underlying principle of which is different from that of conventional analytical instruments, markedly affects many aspects including social economy as well as the food industry.

Keywords: taste sensor, electronic tongue, lipid/polymer membranes, taste scale, potentiometry, allostery

1. Introduction

Various kinds of analytical instruments and methods are indispensable to chemical analyses of materials and chemical substances. These typically include mass spectrometry such as gas or liquid chromatography mass spectrometry (GC/MS or LC/MS), spectroscopic analysis devices such as an ultraviolet visible adsorption spectrophotometer (UV-Vis), nuclear magnetic resonance spectroscopy (NMR), X-ray photon spectroscopy (XPS), electron probe microanalyzer (EPMA), and electrochemical analyzers represented by a pH meter. These analytical devices make it possible to clarify the chemical structure and identify and quantify the chemical species that are constituents of materials. They are very effective for studying the characteristics of objects because all the constituent materials are composed of many kinds of chemical species.

Chemical analyses are carried out to detect and identify chemical substances and species. Let us consider enzyme reactions and antigen–antibody interactions in biological systems from the viewpoint of detection of target materials. An enzyme binds with a ligand on the target, whereas an antibody recognizes a specific antigen. In other words, the selectivity of enzymes and antibodies is very high.

How about the senses of taste and smell in biological systems? The method to detect chemical substances in biological systems through these chemical senses is different from the above. Gustatory and olfactory receptors receive multiple chemical substances of different types simultaneously, but they can barely discriminate one chemical species from others. In fact, one type of sweet receptor receives glucose (monosaccharide) and sucrose (disaccharide) simultaneously, and the receptor does not discriminate between glucose and sucrose. This similar situation holds for the sense of smell; one type of chemical substance binds with multiple receptors of different types, whereas one type of receptor receives several chemical substances of different types. As a result, the odor is recognized first in the brain.

The olfactory sense enables the judgement of whether a chemical substance is harmful to the body

[*1] Institute for Advanced Study/Research and Development Center for Five-Sense Devices, Kyushu University, Fukuoka, Japan.

[†] Correspondence should be addressed to: K. Toko, Institute for Advanced Study/Research and Development Center for Five-Sense Devices, Kyushu University, 744, Motooka, Nishi-ku, Fukuoka 819-0395, Japan (e-mail: toko.kiyoshi.353@m.kyushu-u.ac.jp).

doi: 10.2183/pjab.99.011

Table 1. Main substances and features of seven taste qualities

Taste	Main substances	Feature
Sweetness	Sucrose, glucose, artificial sweetener	Source of energy
Bitterness	Caffeine, theobromine, quinine, humulone, *etc.*	Warning of toxicity
Saltiness	Sodium, potassium, metal cations	Supply of minerals
Sourness	Acids, which supply protons	Activation of metabolism, signal of rotten materials
Umami	Monosodium glutamate, disodium inosinate, disodium guanylate	Supply of indispensable amino acids and nucleotides
Astringency	Compounds of tannin series	Binding to proteins and bitterness receptors on the mucous surface
Pungency	Capsaicin, allyl isothiocyanate, piperine	Binding to heat and pain receptors

or not before it enters the mouth, whereas the gustatory sense enables the judgement of whether a chemical substance is harmful or not once it enters the mouth. For example, sweetness is associated with sources of energy, whereas bitterness is a warning of toxicity. Sweetness, bitterness, saltiness, sourness, and umami are recognized as the five basic taste qualities. Astringency and pungency are not considered basic tastes but are included when considering a wider spectrum of seven basic taste qualities. Table 1 summarizes the main substances and features of the seven taste qualities.[1)–5)]

As is well known, it takes time for a biological system to produce an antibody for a target antigen. Taste and odor substances directly affect the body, and animals including human beings can survive by eating foods, *i.e.*, chemical substances. Animals have to judge instantly whether a chemical substance is poisonous or not in order to live. As a result, animals evolved to first be able to classify substances into harmful or useful ones from the viewpoint of their effect on the body.

In this article, we describe a device used to measure taste, *i.e.*, taste sensors developed by the author. Many review papers on taste sensors have been published so far,[6)–15)] and hence, this article is focused on the measurement principle, its application to foods, and recent developments using modifiers for measuring noncharged bitter substances (xanthine derivatives) such as caffeine and theobromine. Due to their reliance on a potentiometric measurement method, taste sensors have limited ability to detect noncharged substances. Recent taste sensors with the receptive membrane modified with aromatic carboxylic acids on the basis of the allosteric mechanism can measure noncharged bitter substances.

2. Taste sensors: Electronic tongue with global selectivity

Let us look back on the situation for the evaluation of taste in the 1980s when Toko and colleagues started research and development of a taste sensor. Taste was evaluated by food companies to control food quality and develop "palatable food". Taste was also evaluated in the pharmaceutical industry to develop "easy-to-take medicines". Well-trained panelists used to actually eat and evaluate the taste of foods and medicines; hence, individual differences and physical conditions affected the results. In order to remove these disadvantages and obtain objective results, it was necessary to perform a large-scale human sensory evaluation with 15–30 panelists. Furthermore, the sensory evaluation of medicines was sometimes harmful to panelists and is not a pleasant experience. Owing to the low objectivity, low reproducibility, high training cost, and ethical problems, taste evaluation is difficult and takes time. Therefore, a novel evaluation technique that rapidly and easily provides objective results was highly desired. However, very many chemical substances that have taste are included in foods. Moreover, there are interactions between several taste substances or qualities such as suppression or enhancement of taste. The addition of sweet substances to a bitter solution suppresses bitterness, whereas saltiness is enhanced by a small amount of sour substances. It was thought at this time that the practical use of a device to evaluate taste was difficult.

Although several technologies were proposed, they were not put into practical use for the evaluation of tastes composed of the five basic taste

qualities in foods. A pH meter can be used to evaluate sourness, an electric conductivity meter to evaluate saltiness, and a refractometer to evaluate sweetness. However, the data derived from an electric conductivity meter and refractometer are not specific to saltiness and sweetness, respectively. Therefore, they are less useful for foods, which may contain over one thousand types of taste substance. The contribution of each substance to the taste of foods remains uncertain. Furthermore, there are interactions between taste substances or qualities; hence, the detection of such interactions at the reception level is indispensable. No method or sensing device to evaluate taste existed prior to the 1980s. Thus, the first "taste sensor" created high expectations for a sensor to provide a globally applicable common taste scale.

Toko and colleagues performed research on the dynamic electrical properties of lipid membranes in the 1980s, and they applied the results to the sensing of taste.[16)–18)] In 1989, Toko *et al.* filed a patent application for their taste sensor, which utilized a lipid/polymer membrane as the transducer and featured multiarray sensor electrodes.[19),20)] They adopted a development policy focused on global selectivity, which aimed to decompose the characteristics of a chemical substance into taste qualities and quantify them, rather than focusing on individual chemical discrimination.[6)–15)] As demonstrated in Table 1, and mentioned previously, the taste of foods is broken down into various types by each taste receptor in the human tongue. This approach differs from the selectivity principles of chemical/biosensors, which correspond to a specific chemical substance on a one-to-one basis.

The electronic tongue (e-tongue) proposed[21)] in 1995 and many types of e-tongue[22)–39)] using different measurement methods developed afterwards also do not focus on the identification of each chemical substance. Measurement methods using voltammetry, colorimetry, impedance, and gustatory cells have been actively developed in sequence together with the development of sensing materials. Taste sensors to measure liquid samples, such as the e-tongue, are multisensory systems composed of low-selectivity sensors, which utilize multivariate analysis to obtain useful information from multiple sensor outputs. In a method with voltametric measurements, several different types of metallic electrode were adopted in the working electrodes, and then the obtained output patterns were analyzed using principal component analysis (PCA). In a similar way, colorimetric sensor arrays were composed of multiple dyes to chemically respond to taste substances and succeeded in the identification of foods such as beer and soft drinks. Research on sensors using gustatory cells is now very active and hence can be expected as a promising tool in the future. Comparison of these e-tongues and taste sensors including several commercialized sensing systems were made previously.[30),37)] Nowadays, a taste sensor is sometimes called an e-tongue with global selectivity.[11),25),28)]

Fig. 1. Taste sensing system TS-5000Z manufactured by Intelligent Sensor Technology, Inc.

The taste-sensing TS-5000Z system (Fig. 1), developed and marketed by Intelligent Sensor Technology, Inc., uses a receptor membrane composed of a lipid, a plasticizer, and polyvinyl chloride (PVC) to detect taste substances. Multiple lipid/polymer membranes generate potential outputs that quantify the taste of the substance, which can be easily converted into a taste scale due to the logarithmic nature of the sensor response. Since its initial launch in 1993, the TS-5000Z, which was released in 2007, has undergone various improvements, making it a reliable tool for developing new food products, ensuring food quality, and aiding in marketing efforts. With over 600 units in use worldwide, the TS-5000Z has revolutionized the field of taste analysis and visualization.

Table 2 shows a list of lipid/polymer membranes and their compositions, *i.e.*, lipids and plasticizers. They affect the hydrophobicity and electrical charge of the membranes. Sensors to measure the bitterness of medicines (BT0), bitterness of foods (C00), sourness (CA0), umami (AAE), saltiness (CT0), sweetness (GL1), and astringency (AE1) have been put into practical applications. Additionally, two sweetness sensors for artificial sweeteners are still at the

Table 2. Chemical components of each taste sensor

Taste sensor	Lipid	Plasticizer
Bitterness sensor BT0 (for bitter hydrochloride salts)	Phosphoric acid di-n-decyl ester (PADE)	Bis(1-butylpentyl) adipate (BBPA), Tributyl o-acetylcitrate (TBAC)
Bitterness sensor C00 (for acidic bitter substances)	Tetradodecylammonium bromide (TDAB)	2-Nitrophenyl octyl ether (NPOE)
Sourness sensor CA0	Phosphoric acid di(2-ethylhexyl) ester (PAEE), Oleic acid, Trioctylmethylammonium chloride (TOMA)	Dioctyl phenylphosphonate (DOPP)
Umami sensor AAE	Phosphoric acid di(2-ethylhexyl) ester (PAEE), Trioctylmethylammonium chloride (TOMA)	Dioctyl phenylphosphonate (DOPP)
Saltiness sensor CT0	Tetradodecylammonium bromide (TDAB), 1-Hexadecanol	Dioctyl phenylphosphonate (DOPP)
Sweetness sensor GL1 (for noncharged sugars)	Tetradodecylammonium bromide (TDAB), Trimellitic acid	Dioctyl phenylphosphonate (DOPP)
Astringency sensor AE1	Tetradodecylammonium bromide (TDAB)	Dioctyl phenylphosphonate (DOPP)
Sweetness sensor for negatively charged high-potency sweeteners	Tetradodecylammonium bromide (TDAB)	Phosphoric acid tris(2-ethylhexyl) ester (PTEH)
Sweetness sensor for positively charged high-potency sweeteners	Phosphoric acid di-n-decyl ester (PADE)	2-Butoxyethyl oleate (BEO)

research and development stage.[40),41)] The present lipid/polymer membranes are formed targeting specificity to each taste by selecting different compounds and appropriate concentrations. Taste substances interacting with these membranes affect the membrane potential mainly composed of the surface potential generated at the membrane/solution interface. Changes in membrane potential are measured using a potentiometric technology.

The C00 sensor membrane, depicted in Fig. 2, consists of PVC, tetradodecylammonium bromide (TDAB), and 2-nitrophenyl octyl ether (NPOE). This particular sensor is specifically designed to measure the bitterness of food compounds such as iso-α acid. The TDAB molecule's hydrophilic group faces the water phase, whereas the hydrophobic group interacts with PVC through hydrophobic interactions, ensuring thermodynamic stability within the membrane. The surface structure created by this arrangement is crucial in detecting taste substances. Preconditioning using several types of taste solution is essential for realizing this surface structure before the measurement.[42),43)]

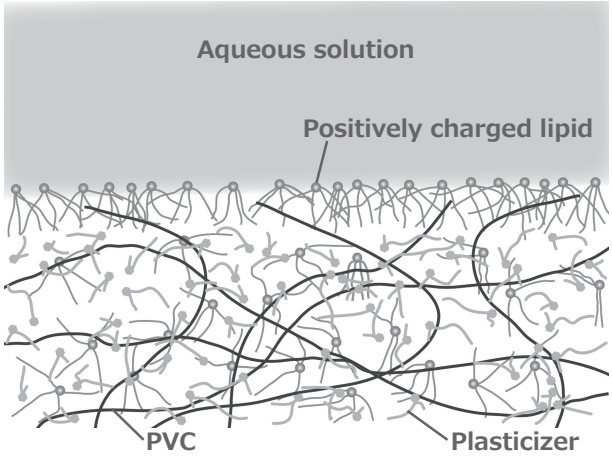

Fig. 2. Schematic of the receptive membrane of bitterness sensor C00 used to measure foods.

The measurement procedure is shown in Fig. 3. The electric potential in the reference solution, which is nearly tasteless, is first measured. The measure-

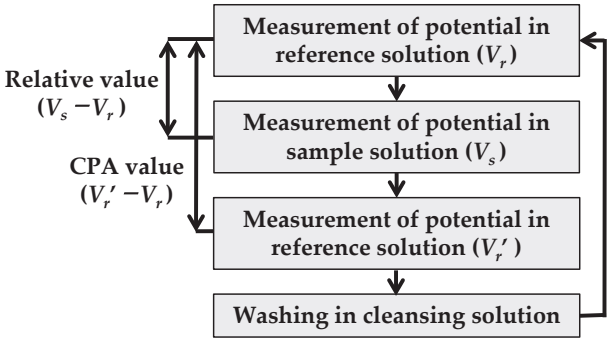

Fig. 3. Measurement procedure for using the taste sensor.

ments are repeated for the potential to become stable so as to satisfy the criterion of a reading below 0.5 mV. Let us denote the obtained potential as V_r. Next, the potential in the sample solution is measured for 20 s. If we denote this potential as V_s, then we call the difference between the two potentials ($V_s - V_r$) the relative value, which corresponds to taste usually felt by humans. After measurement of the sample potential (V_s), the sensor electrode is gently washed and then immersed once more into the reference solution for subsequent measurements. However, during this stage, the membrane does not return to its initial state when the V_r was first recorded because the hydrophobic taste-conferring substances, such as bitterness, astringency, and umami, remain adsorbed onto the membrane. As a result, the potential generated during subsequent measurements (V_r') differs from the initial reference potential (V_r).

The difference ($V_r' - V_r$) indicates the Change in the membrane Potential due to the Adsorption of taste substances onto the membrane (abbreviated as the CPA value). This value depends on both the amount of adsorbed taste substances and the state of the electrical charge of the membrane.[44] The CPA value is a highly selective measure for adsorptive taste substances and does not reflect electrolytic taste qualities, such as saltiness and sourness. Instead, it represents the aftertaste experienced by humans, and thus, by measuring the CPA value, it is possible to quantify the aftertaste associated with the five basic taste qualities. In particular, the food industry involved in the production of broths and soups places significant value on the quantification of "koku" or rich taste, which is mainly attributed to umami substances, because the CPA value is in good agreement with human sensory evaluations.[45] Bitterness in dipeptides and medicines also remains on the tongue, and hence estimates of bitterness becomes possible using the CPA value.[46),47] As the final step, to restore the membrane to its initial state and remove any adsorbed taste substances, the membrane is washed extensively using a designated cleansing solution. This process is essential for reviving the membrane and ensuring accurate subsequent measurements. This cycle of steps to measure V_r, V_s, and V_r' and washing is repeated three to five times.

3. Response characteristics

The taste sensor responses to the five basic taste qualities, including astringency, are presented in Fig. 4.[9)–15)] All samples were prepared using 1 mM KCl as the solvent, and hence the sensor response obtained for 1 mM KCl solution was taken as the origin. The response of the lipid membrane sensor specific to each taste quality, as listed in Table 2, is shown in the graph. The CPA values are shown for BT0, C00, and AE1 in Fig. 4.

According to Fig. 4, the responses demonstrate a proportionality to the concentration's logarithm in certain regions. This finding aligns with human perception, which relates the stimulus intensity to the logarithm of the sensation. The threshold values for each taste quality are as follows: quinine bitterness ranges from 1 to 10 µM, tartaric acid sourness is approximately 0.1 mM, NaCl saltiness ranges from 1 to 10 mM, sucrose sweetness ranges from 3 to 30 mM, and umami (monosodium glutamate: MSG) is approximately 1 mM. The thresholds shown by arrows in Fig. 4 are close to these values.

The bitterness sensor BT0 is highly specific to bitter substances such as quinine, cetirizine, hydroxyzine, and bromhexine, and has a negligible response to sourness, umami, saltiness, sweetness, or astringency. The magnitude of the sensor output varies depending on the intensity of bitterness of the chemical, such that the response is higher for highly bitter substances such as loperamide and lower for mildly bitter ones such as ambroxol. In other words, the BT0 sensor responds proportionally to the bitterness perceived by humans and can be used to quantitatively measure the level of bitterness in a given sample.

Similar results have been obtained for other taste qualities, with the development of high-selectivity membranes and measurement procedures. To achieve membranes that respond only to specific taste qualities, the lipid and plasticizer proportions have been finely tuned. This property depends on achieving a balance between electrical charges and hydrophobicity. For instance, the saltiness sensor CT0 enhances hydrophilicity by increasing the proportion of charged lipid, thereby promoting more electrostatic interactions with ions. Conversely, the bitterness sensor BT0 reduces lipid content, thus increasing hydrophobicity. The use of CPA value is another crucial factor in enhancing selectivity for hydrophobic substances.

Let us discuss the membranes for CT0 and BT0 as examples to demonstrate the selectivity to the five basic taste qualities.[14] Five concentrations of NaCl (10–1000 mM), tartaric acid (0.3–30 mM), quinine hydrochloride (0.01–1 mM), MSG (1–100 mM) and sucrose (30–3000 mM) were set within the range from

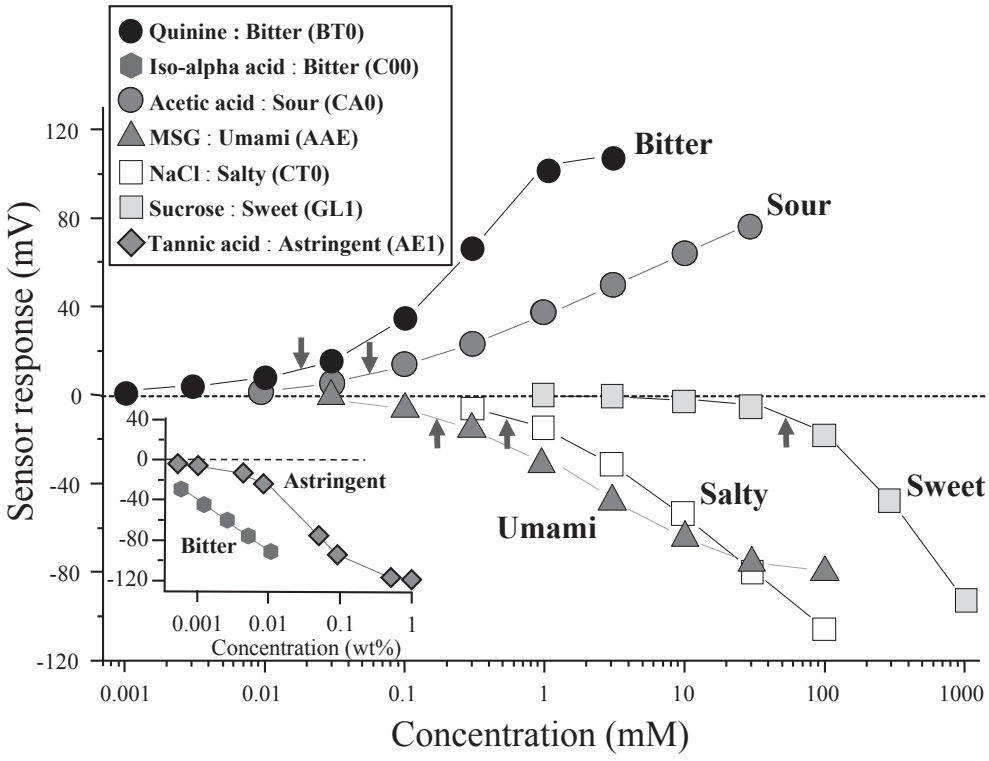

Fig. 4. Responses of the taste sensor to five basic taste qualities and astringency.[13] The detection threshold of each taste quality is shown using an arrow. From Toko *et al.* (2021), reproduced with permission of IOP Publishing Limited through PLSclear.

the human threshold to values one hundred times higher than the threshold. The horizontal axis in Fig. 5 represents an equidistant scale of taste intensity (τ 1, 2, 3, 4, 5) for the five basic taste qualities, where each numerical value on the scale denotes the same subjective taste intensity, regardless of the specific taste quality being evaluated. All the samples included 10 mM KCl as the solvent, and hence the origin of the sensor response was obtained with 10 mM KCl. The comparison of response selectivity as a function of the scale of intensity felt by humans is much different from the usual comparison of selectivity for ions such as Li^+, Na^+, K^+, and Cs^+ or chemical species in the Nicolsky–Eisenman equation. The comparison of ion selectivity is not usually made in the comparison of taste response, because the sensitive concentration region differs largely among taste qualities, as shown in Fig. 4 and in humans, as mentioned above. Figure 5 indicates that the relative value of CT0 increases with the saltiness intensity of NaCl and demonstrates very little sensitivity to the other taste characteristics. The sensor response to NaCl is about −110 mV at 100 mM NaCl in Fig. 4, whereas it is about −60 mV in Fig. 5; this difference was caused by the solvents 1 mM KCl (Fig. 4) and 10 mM KCl (Fig. 5). The almost 50 mV difference, which amounts to the response to 10 mM NaCl in Fig. 4, appeared in Fig. 5. Likewise, the CPA value of BT0 increases solely with the intensity of quinine bitterness. The relationship between the sensor response and taste intensity of NaCl and quinine has been modeled using least-squares regression lines. A similar situation holds for other taste qualities such as umami (AAE), bitterness (C00), sourness (CA0), sweetness (GL1), and astringency (AE1), as reported previously.[9)–11)] These results imply that each sensor has taste-specific sensitivity.

4. Response mechanism

As stated above, the selectivity to each taste quality was obtained by controlling the balance between electrical charges and hydrophobicity and measuring the CPA value. The mechanism by which the lipid/polymer membranes change their electric potentials upon the application of taste substances was also clarified on the basis of an electrochemical theory.[48)] In a broad sense, taste sensors are ion

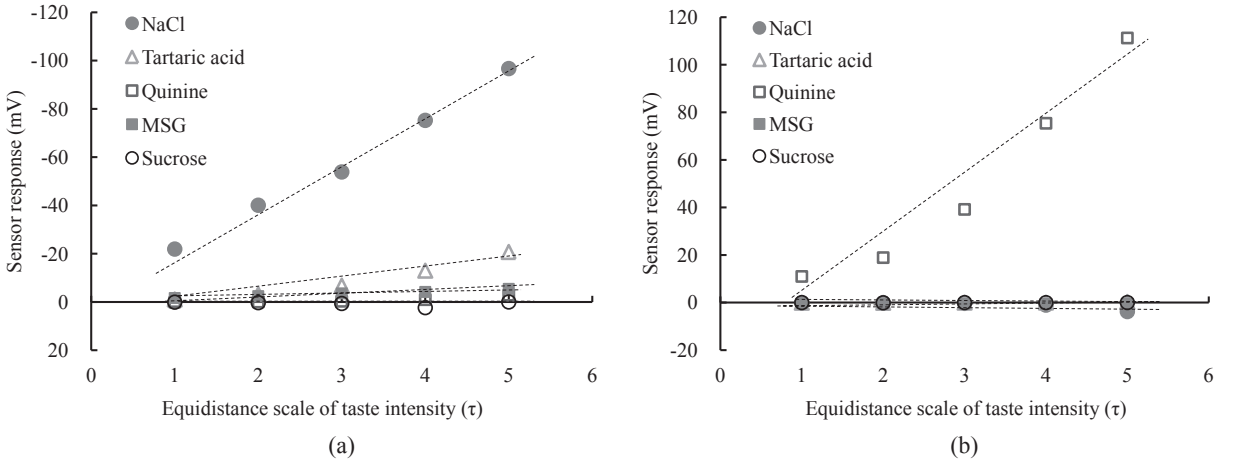

Fig. 5. Responses of (a) saltiness sensor CT0 (relative values) and (b) bitterness sensor BT0 (CPA values) to five basic tastes.[14] Reprinted from Wu and Toko (2023) with permission from Elsevier.

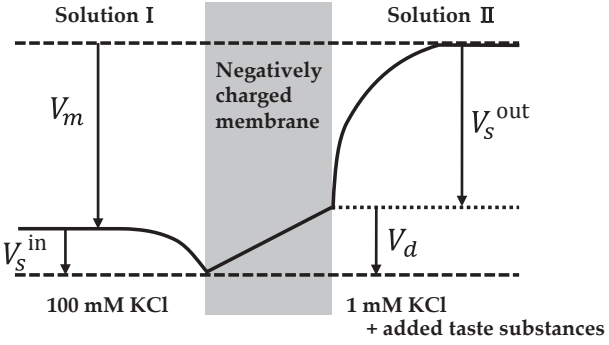

Fig. 6. Electric potential profile in a negatively charged membrane system.

selective electrodes fabricated using PVC matrix membranes based on ion-exchangers. The potential profile is illustrated in Fig. 6. Here, we consider the lipid/polymer membrane composed of a lipid phosphoric acid di(2-ethylhexyl) ester (PAEE), a plasticizer dioctyl phenylphosphonate (DOPP), and PVC as a typical negatively charged membrane. This membrane is not used at present, but it is helpful in elucidating the response mechanism underlying the lipid/polymer membranes of the current taste sensors. The charged membrane acts as a barrier between two KCl solutions, labeled I and II, with the outer solution II containing the taste substances. The membrane potential is composed of the electric potential at the aqueous interface of the membrane and the potential due to ion diffusion within the membrane. The effects of salty and bitter substances, NaCl and quinine hydrochloride, respectively, on the membrane potential are considered here.

The membrane potential V_m defined in Fig. 6 is expressed by

$$V_m = V_s^{\text{out}} + V_d - V_s^{\text{in}}, \quad [1]$$

where V_s^{out} and V_s^{in} are the surface electric potential formed in the aqueous phase of the outer and inner sides across the membrane, respectively, and V_d is the diffusion potential.

To explain the response to taste substances, it is necessary to consider the relationship between the change in the surface potential V_s^{out} and the ion concentration in the outer bulk solution. This can be achieved by taking into account the change in the surface charge density σ, which is caused by the hydrophilic groups of the lipid of the membrane facing the aqueous phase. Specifically, when H^+ dissociates from lipid molecules, it causes a change in the electric charge density σ, leading to a change in the surface electric potential V_s^{out}. This process is similar to what occurs in lipid membranes or colloidal systems.[49)–51)]

To determine the charge density σ at the membrane surface, the Gouy–Chapman theory of the electrical double layer is employed as the simplest approximation. The Poisson–Boltzmann equation is then solved to calculate the ion distribution near the membrane surface and the surface charge density σ. By taking into account the boundary conditions, we obtain the expression for σ as a function of V_s^{out}

$$\sigma = \kappa' \sinh\left(\frac{eV_s^{\text{out}}}{2k_{\text{B}}T}\right); \quad [2]$$

$$\kappa' = \frac{\varepsilon}{2\pi}\frac{k_{\mathrm{B}}T}{e}\kappa, \quad \kappa = \sqrt{\frac{8\pi c e^2}{\varepsilon k_{\mathrm{B}}T}}, \qquad [3]$$

where c denotes the ion concentration in the bulk solution containing Na^+ or quinine ions, ε the dielectric constant, e the elementary charge, k_{B} the Boltzmann's constant, and T the absolute temperature.

The inverse of the parameter κ in Eq. [3], $1/\kappa$, can be regarded as the thickness of the diffuse double layer. Its value reduces with increasing ion concentration and shows values of roughly 10, 3, and 1 nm for 1, 10, and 100 mM solutions of NaCl, in this order.

The electrolyte NaCl affects the electrical double layer, and the surface electric potential V_s^{out} can be changed. Using the degree of H^+ binding θ, we can express the surface charge density σ as

$$\sigma = -\frac{e}{A}(1-\theta), \qquad [4]$$

where A is the occupied molecular surface area per lipid molecule.

By minimizing the Gibbs free energy in the charged membrane system with respect to θ by taking account of Eq. [4], we obtain the following equation:

$$\frac{\theta}{1-\theta} = \frac{[\mathrm{H}^+]}{K}\exp\left(\frac{-eV_s^{\mathrm{out}}}{k_{\mathrm{B}}T}\right), \qquad [5]$$

where $[H^+]$ is the H^+ concentration in the bulk solution and K is the dissociation constant.

The variables σ, θ, and V_s^{out} are calculated using the three Eqs. [2], [4], and [5]. Therefore, the surface potential V_s^{out} of the membrane directly related to the measurement can be obtained as a function of the NaCl concentration c.

When quinine hydrochloride is contained in the taste solution, its hydrophobic character causes it to bind to the hydrophobic portion of the membrane. Therefore, the surface charge density σ of the membrane is easily changed by binding of charged quinine. The expression for σ becomes

$$\sigma = -\frac{e}{A}(1-\theta) + \frac{e}{A}\theta_q. \qquad [6]$$

Here, θ_q represents the degree of binding of quinine ions, which depends on both the quinine concentration near the membrane surface and the electric charge state of the membrane. The expression for θ_q is therefore established:

$$\theta_q = a(1-\theta)^2 c_q \exp\left(\frac{-eV_s^{\mathrm{out}}}{k_{\mathrm{B}}T}\right), \qquad [7]$$

with the bulk quinine concentration c_q, and a numerical parameter denoted by a. For factor $(1-\theta)^2$, it is assumed that more quinine ions are bound to the membrane when the degree of H^+ binding is low because there exist more non-occupied sites at the surface. The surface potential V_s^{out} can be calculated using Eqs. [2], [6], and [7] for the case containing quinine.

Next, we will now contemplate the diffusion potential V_d within the membrane, which stems from the dissimilarity in the mobility of cations and anions. In the case of ion selective electrodes with PVC matrix membranes based on ion-exchangers, the surface potential contributes to most of the response potential, as concluded in several reports.[52),53)] Ions can hardly permeate through a lipid/polymer membrane made of PAEE. This conclusion can be acknowledged because the membrane electric resistance is as high as over 1 MΩ·cm^2. In this high-resistance state, ion permeability cannot be expected. The change in V_d is not necessary to consider. The surface potential V_s^{in} is of course constant.

Figure 7 shows the comparison of theoretical results with the observed response potentials of the PAEE membrane, where the lines represent the theoretical results, circles and squares denoting experimental data[54)] on NaCl and quinine, respectively. The theoretical data agree quantitatively with the observed data. The parameter values were chosen to explain the experimental results in the best fit within their reasonable ranges: $K = 10^{-4}$ M, $A = 1.2$ nm^2, and $a = 150$. The occupied molecular surface area A was estimated from the volume of the membrane and the amount of lipid PAEE used.

The theoretical results[48)] of the surface charge density σ and the degree of H^+ binding θ showed that the membrane made of PAEE is not highly electrically charged at low ionic strengths and then becomes more negatively charged by H^+ dissociation that is accelerated with increasing NaCl concentration. The dense packing of lipid molecules in the membrane inhibits the dissociation of H^+ from the hydrophilic group of the lipid, which creates a significant electrical repulsion between charged lipid molecules. The electric screening upon the addition of NaCl enables H^+ dissociation. The essentially same phenomena are observed in other systems.[50),55),56)]

The above calculation is related to the relative values defined in Fig. 3. Similar evaluations of CPA

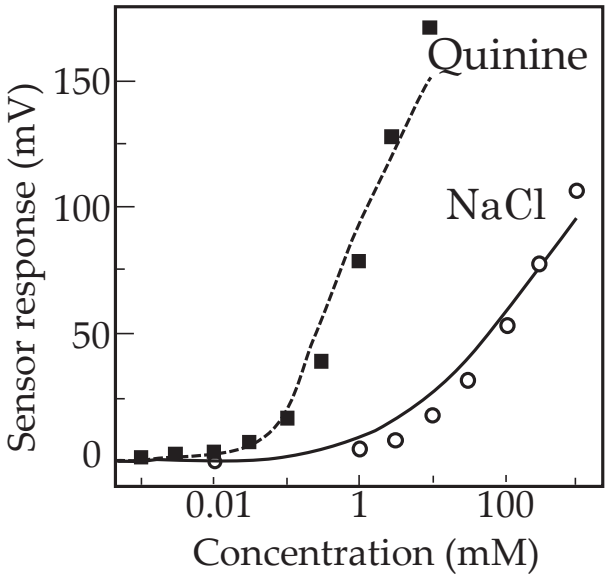

Fig. 7. Comparison of theoretical results with observed data. Data on NaCl and quinine are shown as open circles (○) and closed squares (■), respectively. The theoretical results are shown as solid and dashed lines.

values, *e.g.*, resulting from quinine binding, are possible in principle, by adopting θ_q as the initial value in the surface charge density σ in Eq. [6] when the membrane is immersed in the reference solution.

5. Taste sensor based on allostery for noncharged substances

Allostery is a phenomenon that occurs in many enzymes and receptors including taste receptors, where binding with a ligand at one site affects binding with a different or the same type of ligand at another distant site of the enzyme or receptor molecule.[57)–59)] As previously discussed, BT0 and C00 sensors demonstrate high sensitivity and selectivity to bitter substances in medicines and foods, as reflected in their CPA values. However, because these sensors rely on potentiometric measurement, the potential change arises mainly from alterations in surface charge density induced by interactions with charged substances. As a result, both the BT0 and C00 sensors are insensitive to noncharged substances. Recently, a novel type of taste sensor based on allostery has been developed to detect noncharged bitter substances such as caffeine and theobromine.[60)–63)] Modifying the surface of the lipid/polymer membrane with an aromatic carboxylic acid creates a hydroxy group that interacts with caffeine molecules. This interaction ultimately affects the H^+ dissociation of a carboxy group at a separate site on the membrane surface. This, in turn, causes an increase in surface charge density, resulting in an elevation of membrane potential.

Caffeine, an alkaloid belonging to the purines, is contained mainly in tea leaves and coffee beans. It is a type of xanthine derivative, which is an aromatic heterocyclic organic compound consisting of a pyrimidine ring and an imidazole ring. Although alkaloids are typically basic nitrogen compounds, caffeine lacks basic properties and is therefore noncharged.

In our prior research,[60)–63)] we focused on developing a new sensor capable of detecting noncharged bitter substances like xanthine derivatives (*e.g.*, caffeine, theophylline, and theobromine), which are frequently present in drinks and medicinal items. To do so, we created a sensor electrode composed of a membrane containing lipid TDAB, the plasticizer DOPP, and PVC, which was then modified by immersing it in a solution containing 0.05 wt% of 2,6-dihydroxybenzoic acid (2,6-DHBA).

The taste sensor developed in this study demonstrated a strong correlation with sensory tests for caffeine at various concentrations (1, 3, 10, and 30 mM), with an R^2 value of 0.94. Additionally, the sensor exhibited high correlations of 0.90 and 0.81 for theobromine and theophylline, respectively. The sensor exhibited high sensitivity and selectivity towards caffeine, displaying the largest response (about 50 mV) to caffeine, while showing only about 15 mV in response to sourness and negligible responses (less than 5 mV) to other taste samples. Although the sensor did respond to sourness, this effect could be eliminated by using the bitterness sensor developed in this study in conjunction with a commercially available sourness sensor, as previously reported for substances that contain both sweetness and bitterness or saltiness.[14),15)]

The sensor used in this study had lipid/polymer membranes modified with 0.05 wt% aromatic carboxylic acid, and its response to caffeine was measured in the range of 1–100 mM in the reference solution.[60)] The results, depicted in Fig. 8, showed that two membranes modified with 2,6-DHBA or 2,4,6-trihydroxybenzoic acid (2,4,6-THBA) exhibited notable responses to caffeine. Moderate responses to caffeine were observed in the two membranes modified with 2,3-dihydroxybenzoic acid (2,3-DHBA) or 2,5-dihydroxybenzoic acid (2,5-DHBA). As the concentration of caffeine increased, these responses increased. However, the other three membranes that were

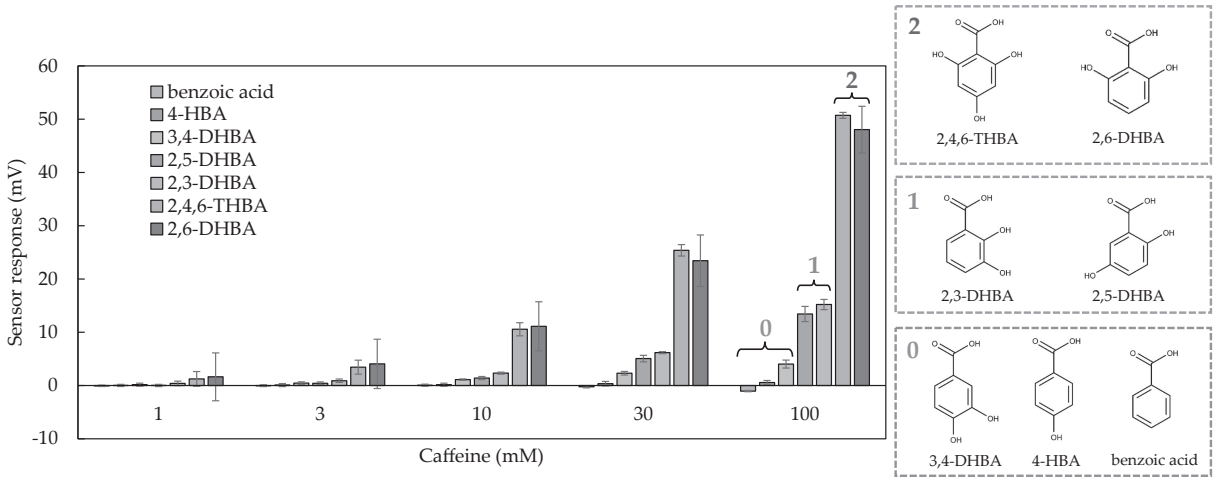

Fig. 8. Responses of membranes formed using the surface modification method with seven aromatic carboxylic acids to 100 mM caffeine.[60] The numerical figures "2", "1", and "0" indicate the number of intramolecular H bonds. Reprinted from Yoshimatsu *et al.* (2020).

treated with 3,4-dihydroxybenzoic acid (3,4-DHBA), benzoic acid, or 4-hydroxybenzoic acid (4-HBA) did not exhibit any response to caffeine.

These results can be explained by considering the properties of aromatic carboxylic acids.[64),65)] For 2,6-DHBA and 2,4,6-THBA, caffeine binding with the hydroxy groups breaks two intramolecular H bonds of the substances, resulting in the carboxy group taking back dissociated H^+ from the solution. This leads to an increase in the surface charge density of the membrane, which in turn causes an increase in membrane potential. For 2,3-DHBA and 2,5-DHBA, which have only one intramolecular H bond, the change in surface charge density is smaller than that in the case of 2,6-DHBA and 2,4,6-THBA. Finally, 3,4-DHBA, 4-HBA, and benzoic acid showed no response to caffeine since they lack intramolecular H bonds. These results and interpretations suggest that the configuration of a molecular structure with carboxy and hydroxy groups on both sides, and an intramolecular H bond, is effective in inducing a response to caffeine.

The effect of the intramolecular H bond is found in the acid dissociation constant (pKa). The pKa values of benzoic acid, 4-HBA, 3,4-DHBA, 2,3-DHBA, 2,5-DHBA, 2,4,6-THBA, and 2,6-DHBA are 4.08, 4.38, 4.16, 2.56, 2.53, 1.95, and 1.64, respectively. Further evidence supporting the formation of intramolecular H-bonds can be found in the cocrystallization behavior of aromatic carboxylic acids. Specifically, 2,3-, 2,4-, 2,5-, 3,4-, and 3,5-DHBA form cocrystals with piracetam, whereas 2,6-DHBA does not,[66)] likely because of two intramolecular H bonds formed between the hydroxy groups and carboxy group of the molecule.

Moreover, recent research[62),63)] has suggested that both the response to caffeine and reference potential are influenced by the partition coefficient ($\log P$) and pKa of the HBAs. Notably, a sensor modified with 2,6-DHBA demonstrated high sensitivity to caffeine in the region where the reference potential sharply decreased with increasing 2,6-DHBA concentration.

The above response mechanism was confirmed by ^{1}H NMR. The results obtained from the taste sensor and ^{1}H NMR analysis for the five modifiers are presented in Table 3.[61)] It was observed that caffeine interacts with all three HBAs and resorcinol, but the sensor modified with 2,6-DHBA exhibited a substantial response. The membrane potential change was moderate with 2-HBA and almost negligible with 3,5-DHBA, as shown in Table 3. The discussion

Table 3. Summary of taste sensor and ^{1}H NMR results.[61)] Reprinted from Ishida *et al.* (2022)

	Sensor response	Interactions investigated by ^{1}H NMR
2,6-DHBA	52 mV	Yes
2-HBA	15 mV	Yes
3,5-DHBA	7 mV	Yes
Resorcinol	3 mV	Yes
Aniline	−2 mV	No

similar to the above holds on these three modifiers, 2,6-DHBA, 2-HBA and 3,5-DHBA, which surely interact with caffeine.

The change in chemical shift occurred in resorcinol. These results for the three HBAs and resorcinol suggest that the hydroxy group of modifiers participates in the interaction with caffeine. It is quite reasonable that the resorcinol-modified sensor did not show much response to caffeine, because resorcinol lacks a carboxy group that would allow for the formation of intramolecular hydrogen bonds in the same way as 3,5-DHBA. Similarly, aniline, which lacks a hydroxy group, does not interact with caffeine and therefore does not elicit a response from the taste sensor. The presence of intramolecular hydrogen bonds in HBA is necessary for the taste sensor to effectively measure the bitterness of caffeine, as confirmed by both the taste sensor and ^{1}H NMR results.

We conducted nuclear Overhauser effect spectroscopy (NOESY) measurement to identify the type of bond formed in the interaction.[61] We can predict that caffeine and 2,6-DHBA have a stacked structure as shown in Fig. 9 by taking into account two facts, *i.e.*, "the hydroxy group of HBA participates in the interaction", as shown by the ^{1}H NMR results, and "protons are close to each other", as shown by the NOESY results. The reports regarding cocrystals provide evidence that supports the aforementioned prediction, specifically that the hydroxy group of HBA forms hydrogen bonds with the carbonyl group (=O) or N (imidazole) of caffeine. The interaction between caffeine and 2,6-DHBA was found to occur through the formation of hydrogen bonds between the hydroxy group of HBA and the carbonyl group or N (imidazole) of caffeine, in addition to the $\pi - \pi$ interaction between the aromatic rings.

To summarize, at the surface of the membrane in the reference solution, two intramolecular hydrogen bonds are formed between one COO^- group and two OH groups of 2,6-DHBA. When the sensor electrode is submerged in a taste solution containing caffeine, the carbonyl group of caffeine can potentially form a hydrogen bond with the hydroxy group of 2,6-DHBA, specifically an O–HO bond.[67] This interaction leads to the disruption of the pre-existing intramolecular hydrogen bonds in 2,6-DHBA, resulting in an unstable H^+ dissociation state of the carboxy group. As a result, a 2,6-DHBA molecule becomes electrically neutral by accepting H^+ from the solution, leading to an increase in the membrane potential.

This measurement utilizing allostery is based on a newly found mechanism of potentiometry. The sensitivity may be increased by choosing modifiers with lower pKa and higher log *P*.[63] The present results provide a novel sensing mechanism by which an aromatic carboxylic acid contained in the receptive membrane binds with noncharged bitter substances through H bonds and $\pi - \pi$ interaction to induce the H binding at a distant carboxy group of the modifier.

6. Application to foods

Taste sensors are presently employed for assessing a range of foods and drinks such as coffee,[13,68–71] green tea,[72–74] ginseng tea,[75] black tea,[76] beer,[77–79] sake,[80] wine,[81] water,[82] juice,[83] milk,[84–86] soup,[45] soy sauce,[87] amino acids,[88] and dipeptides.[46] In addition to food and beverages, bitterness sensors are utilized for assessing the bitterness of medicines in research study and product development.[47,89–93]

Figure 10 illustrates a taste map that evaluates world beers based on the readings of bitterness and sourness sensors, namely C00 and CA0, respectively. The vertical axis of the map represents the intensity of bitterness, which is indicative of the "malt taste". On the other hand, the horizontal axis represents

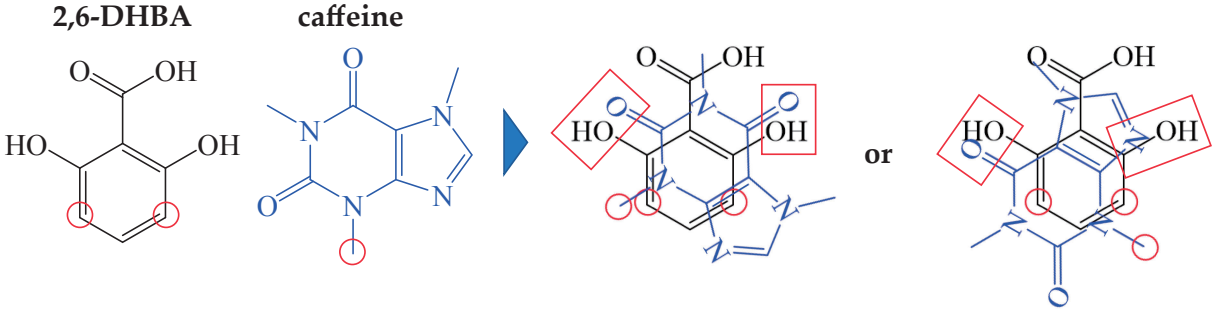

Fig. 9. Prediction of the binding form of 2,6-DHBA and caffeine.[61] Reprinted from Ishida *et al.* (2022).

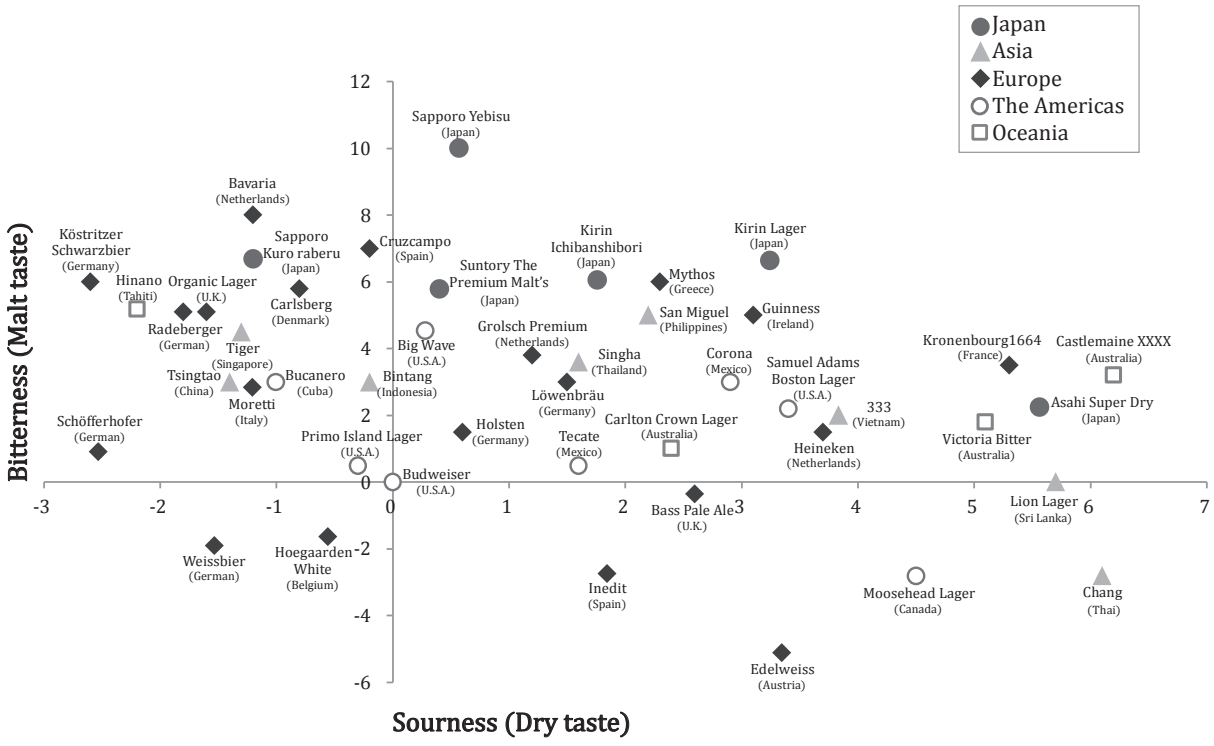

Fig. 10. Taste map of world beers.

the intensity of sourness, which is representative of the "dry taste". The scales for bitterness and sourness are clearly marked on the taste map, where each scale unit denotes the minimum difference in taste intensity that can be perceived by humans. Specifically, a difference of one scale unit is equivalent to a 1.2-fold increase in concentration of iso-α acid (for bitterness) and tartaric acid (for sourness). If the difference between two taste intensities is over two scale units, it is considered to be significant. This "taste scale" can be obtained by a proportional calculation using the response values of the taste sensors.

According to Fig. 10, Sapporo Yebisu (Japan) and Bavaria (Netherlands) beers exhibited a pronounced bitter taste. In order to make a comparison with other beers, Budweiser (U.S.A.) was selected as a representative. On the other hand, Edelweiss (Austria), Inedit (Spain), Hoegaarden White (Belgium), and Weissbier (Germany) beers possessed a very mild bitterness. As for the sourness component, Asahi Super Dry (Japan), Chang (Thai), Kronenbourg 1664 (France), and Castlemaine XXXX (Australia) beers were noted to have a sour taste. Because the taste sensor can measure six kinds of taste quality, the presentation of the taste of foods is also made using a radar chart composed of these axes indexed by each taste quality.[9),11),15)] Thus, we are able to visualize the taste using this approach.

7. Future prospects

The development and principle of taste sensors and their applications to foods have been described in this article, and a novel type of taste sensor using allostery for noncharged bitter substances was explained in detail. Six hundred commercialized taste sensors are now being utilized for evaluating the taste of foods and medicines. The taste sensors are widely used in food and pharmaceutical companies to digitize taste felt by humans, the underlying principle of which is different from that of conventional analytical instruments. Nevertheless, current taste sensors cannot measure noncharged taste substances such as caffeine because they are based on potentiometric measurement. However, as for noncharged sweet substances, the measurement has become possible by modifying the lipid/polymer membrane with aromatic carboxylic acids such as trimellitic acids.[94)–97)] The sensor for noncharged sweet substances is GL1 listed in Table 2. The problem of noncharged bitter substances is now being solved using allostery. The phenomena based on the

allosteric mechanism has been reported for G protein-coupled receptors (GPCR)[57)–59)] that receive photons, hormones, neurotransmitters, odor substances, and taste substances. Therefore, the application of allostery to taste sensors is not unusual at all. The present results promote the practical use of taste sensors using allostery and their application to general biosensing.

A collaborative effort between Itochu Corporation, the Taste & Aroma Strategic Research Institute Co., Ltd., and WingArc1st Inc. has resulted in the development of a digital transformation (DX) support service called "FOODATA" (https://www.itochu.co.jp/en/news/press/2021/210709.html). This service utilizes a database of taste information obtained from taste sensors and is designed to assist with the planning and development of food products. By combining "product data" related to taste, nutrition, and ingredients of food with "human data" on consumer behaviors and preferences such as identification point-of-sale (ID-POS) data, awareness, and reviews, FOODATA serves as a data analysis tool for the food industry. The use of FOODATA allows food companies to address three key challenges in the product planning and development process: 1) providing evidence to support intuitions and experiences, 2) reducing the time required for analysis, and 3) minimizing the cost of data acquisition. FOODATA provides an environment for evaluating ideas and supports the improvement of a product plan, ultimately enhancing the product development capabilities of food companies while increasing the efficiency of the supply chain and reducing losses such as food waste.

The taste-sensor technology markedly affects many aspects including social economy as well as the food industry. The taste database obtained from taste sensors is utilized in a wide range of research and development of drinks, processed foods, and seasoning, agricultural, livestock, and pharmaceutical products. Food companies can determine the favorite trends of consumers using the taste database, which becomes the standard of product choice for the consumers. The impact of taste-sensor technology will continue in the future. Various types of lifestyle to avoid crowding are recommended owing to the corona virus disease (COVID-19) pandemic. However, panelists with training always check the taste and quality of foods in food factories. This situation will be drastically improved by the spread of taste sensors together with odor sensors (e-noses) and other types of sensor. Sight and sound information can be transmitted to distant locations through devices (displays and speakers) to currently express available sight and hearing, as well as sensors (cameras and microphones). Information including taste and smell can, therefore, now be transmitted to distant locations. Integration of plural outputs from these different types of sensor and instrument enables the expression of low-level Kansei words such as sweetness, sourness, the odor of apple, red apple, the scent of roses and crunchy. Then, high-level Kansei words such as watery, fruity, heavy, ripe, and rotten can be obtained using artificial intelligence (AI) and multivariate analyses. This process leads to the final evaluation, *i.e.*, palatable or not. It means that the spread of sensors to detect the five senses enables the design of palatable foods as well as quality control in terms of taste and smell in many factories, regardless of the location of evaluators at home and elsewhere, at one place simultaneously.

We face the need of developing nutritious delicious food for the superaged society, the diversity of palatability in a globalized society, and the widespread use of e-commerce and delivery services in response to COVID-19. Taste sensors enable the preparation of meals taking into account individual palatability by visualization of taste. Innovation in the food industry will overcome the long-time problems for food, and as a result, contributing to the future creation of societies with individuals who can enjoy meals and health throughout life across generations and national borders.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP21H05006 and a project commissioned by the New Energy and Industrial Development Organization (NEDO).

References

1) Beidler, L.M. (1971) Part 2; Taste. *In* Handbook of Sensory Physiology. Vol. 4: Chemical Senses (ed. Beidler, L.M.). Springer-Verlag, Berlin, pp. 200–220.
2) Pfaffmann, C. (1959) The sense of taste. *In* Handbook of Physiology. Section 1: Neurophysiology (eds. Williams, J. Field. and Baltimore, W.). American Physiological Soc., Rockville, Vol. 1, pp. 507–533.
3) Indow, T. (1966) A general equi-distance scale of the four qualities of taste. Jpn. Psychol. Res. **8**, 136–150.
4) Herrmann, K. (1972) Taste of food especially more bitter or sweeter, and its relationship to the chemical structure of taste giving substances.

Ernahr.-Umsch. **19**, 251–256.
5) Yamaguchi, S. (1987) Fundamental properties of umami in human taste sensation. *In* Umami: A Basic Taste (eds. Kawamura, Y. and Kare, M.R.). Marcel Dekker, Inc., New York and Basel, pp. 41–73.
6) Toko, K. (1996) Taste sensor with global selectivity. Mater. Sci. Eng. C **4**, 69–82.
7) Toko, K. (2000) Taste sensor. Sens. Actuators B Chem. **64**, 205–215.
8) Toko, K. (2000) Biomimetic Sensor Technology. Cambridge Univ. Press, Cambridge, pp. 113–195.
9) Kobayashi, Y., Habara, M., Ikezazki, H., Chen, R., Naito, Y. and Toko, K. (2010) Advanced taste sensors based on artificial lipids with global selectivity to basic taste qualities and high correlation to sensory scores. Sensors (Basel) **10**, 3411–3443.
10) Tahara, Y. and Toko, K. (2013) Electronic tongues – A review. IEEE Sens. J. **13**, 3001–3011.
11) Toko, K., Tahara, Y., Habara, M., Kobayashi, Y. and Ikezaki, H. (2016) Taste sensor: Electronic tongue with global selectivity. *In* Essentials of Machine Olfaction and Taste (ed. Nakamoto, T.). Wiley, State of New Jersey, pp. 87–174.
12) Wu, X., Tahara, Y., Yatabe, R. and Toko, K. (2020) Taste sensor: Electronic tongue with lipid membranes. Anal. Sci. **36**, 147–159.
13) Toko, K., Tahara, Y., Habara, M. and Ikezaki, H. (2021) Potentiometric electronic tongue using lipid/polymer membrane. *In* Electronic Tongues (eds. Shimizu, F.M., Braunger, M.L. and Riul, A. Jr.). IOP Publishing, Philadelphia, pp. 2-1–2-28.
14) Wu, X. and Toko, K. (2023) Taste sensor with multiarray lipid/polymer membranes. Trends Analyt. Chem. **158**, 116874.
15) Toko, K. (2023) Recent development of taste sensors. Food Sci. Technol. Res. **29**, 87–99.
16) Toko, K., Nitta, J. and Yamafuji, K. (1981) Dynamic aspect of a phase transition in DOPH-Millipore membranes. J. Phys. Soc. Jpn. **50**, 1343–1350.
17) Iiyama, S., Toko, K. and Yamafuji, K. (1986) Effect of bitter substances on a model membrane system of taste reception. Agric. Biol. Chem. **50**, 2709–2714.
18) Iiyama, S., Toko, K., Hayashi, K. and Yamafuji, K. (1989) Effect of several sweet substances on the electric characteristics of a dioleyl phosphate-Millipore membrane. Agric. Biol. Chem. **53**, 675–681.
19) Hayashi, K., Yamanaka, T., Toko, K. and Yamafuji, K. (1990) Multichannel taste sensor using lipid membranes. Sens. Actuators B Chem. **2**, 205–213.
20) Yamafuji, K., Toko, K. and Hayashi, K. (1996) Taste sensing system using artificial lipid membranes, EP 0410356 B1, Application number: 90114098.8, Priority: 24.07.1989 JP 190819/89, Grant of patent: 1996.03.06.
21) Natale, C.D., D'Amico, A., Vlasov, Y.G., Legin, A.V. and Rudnitskaya, A.M. (1995) Multicomponent analysis of heavy metal cations and inorganic anions in liquids by a non-selective chalcogenide glass sensor array. *In* Proceedings of the International Conference Eurosensors IX, Stockholm, pp. 36–37.
22) Geary, J. (2002) The Body Electric: An Anatomy of the New Bionic Senses. Rutgers University Press, New Brunswick (New Jersey), pp. 85–99.
23) Sehra, G., Cole, M. and Gardner, J.W. (2004) Miniature taste sensing system based on dual SH-SAW sensor device: An electronic tongue. Sens. Actuators B Chem. **103**, 233–239.
24) Ciosek, P. and Wróblewski, W. (2007) Sensor arrays for liquid sensing – Electronic tongue systems. Analyst (Lond.) **132**, 963–978.
25) Anand, V., Kataria, M., Kukkar, V., Saharan, V. and Choudhury, P.K. (2007) The latest trends in the taste assessment of pharmaceuticals. Drug Discov. Today **12**, 257–265.
26) Winquist, F. (2008) Voltammetric electronic tongues – Basic principles and applications. Microchim. Acta **163**, 3–10.
27) Escuder-Gilabert, L. and Peris, M. (2010) Review: Highlights in recent applications of electronic tongues in food analysis. Anal. Chim. Acta **665**, 15–25.
28) Riul, A. Jr., Dantas, C.A.R., Miyazaki, C.M. and Oliveira, O.N. Jr. (2010) Recent advances in electronic tongues. Analyst (Lond.) **135**, 2481–2495.
29) Ghasemi-Varnamkhasti, M., Mohtasebi, S.S. and Siadat, M. (2010) Biomimetic-based odor and taste sensing systems to food quality and safety characterization: An overview on basic principles and recent achievements. J. Food Eng. **100**, 377–387.
30) Woertz, K., Tissen, C., Kleinebudde, P. and Breitkreutz, J. (2011) A comparative study on two electronic tongues for pharmaceutical formulation development. J. Pharm. Biomed. Anal. **55**, 272–281.
31) Woertz, K., Tissen, C., Kleinebudde, P. and Breitkreutz, J. (2011) Taste sensing systems (electronic tongues) for pharmaceutical applications. Int. J. Pharm. **417**, 256–271.
32) Savage, N. (2012) The taste of things to come. Nature **486**, 18–19.
33) Sharma, G., Kumar, S., Kumar, A., Sharma, A., Kumar, R., Kaur, R. *et al.* (2015) Development of lipid membrane based taste sensors for electronic tongue. Procedia Comput. Sci. **70**, 146–152.
34) Podrażka, M., Bączyńska, E., Kundys, M., Jeleń, P.S. and Nery, E.W. (2018) Electronic tongue – A tool for all tastes? Biosensors **8**, 3390.
35) Riul, A. Jr. and Correa, D.S. (2021) A first taste to electronic tongues. *In* Electronic Tongues (eds. Shimizu, F.M. Braunger, M.L. and Riul, A. Jr.). IOP Publishing, Philadelphia, pp. 1-1–1-4.
36) Tian, Y., Wang, P., Du, L. and Wu, C. (2022) Advances in gustatory biomimetic biosensing technologies: In vitro and in vivo bioelectronic tongue. Trends Analyt. Chem. **157**, 116778.
37) Pein, M., Kirsanov, D., Ciosek, P., del Valle, M., Yaroshenko, I., Wesoły, M. *et al.* (2015) Inde-

pendent comparison study of six different electronic tongues applied for pharmaceutical analysis. J. Pharm. Biomed. Anal. **114**, 321–329.
38) Banerjee, R., Tudu, B., Bandyopadhyay, R. and Bhattacharyya, N. (2016) A review on combined odor and taste sensor systems. J. Food Eng. **190**, 10–21.
39) Shimizu, F.M., Gaál, G., Braunger, M.L. and Riul, A. Jr. (2021) Recent developments on devices applied to impedimetric electronic tongues. *In* Electronic Tongues (eds. Shimizu, F.M. Braunger, M.L. and Riul, A. Jr.). IOP Publishing, Philadelphia, pp. 7-1–7-19.
40) Yasuura, M., Okazaki, H., Tahara, Y., Ikezaki, H. and Toko, K. (2014) Development of sweetness sensor with selectivity to negatively charged high-potency sweeteners. Sens. Actuators B Chem. **201**, 329–335.
41) Yasuura, M., Tahara, Y., Ikezaki, H. and Toko, K. (2014) Development of a sweetness sensor for aspartame, a positively charged high-potency sweetener. Sensors (Basel) **14**, 7359–7373.
42) Harada, Y., Noda, J., Yatabe, R., Ikezaki, H. and Toko, K. (2016) Research on the changes to the lipid/polymer membrane used in the acidic bitterness sensor caused by preconditioning. Sensors (Basel) **16**, 230.
43) Yatabe, R., Noda, J., Tahara, Y., Naito, Y., Ikezaki, H. and Toko, K. (2015) Analysis of a lipid/polymer membrane for bitterness sensing with a preconditioning process. Sensors (Basel) **15**, 22439–22450.
44) Toko, K., Hara, D., Tahara, Y., Yasuura, M. and Ikezaki, H. (2014) Relationship between the amount of bitter substances adsorbed onto lipid/polymer membrane and the electric response of taste sensors. Sensors (Basel) **14**, 16274–16286.
45) Doi, M. (2011) Evaluation of kokumi taste of Japanese soup stock materials using taste sensor. Sens. Mater. **23**, 493–499.
46) Guo, J., Hirasaki, N., Miyata, Y., Tanaka, K., Tanaka, T., Wu, X. *et al.* (2016) Evaluating the reduced hydrophobic taste sensor response of dipeptides by theasinensin a by using NMR and quantum mechanical analyses. PLoS One **11**, 1–14.
47) Harada, T., Uchida, T., Yoshida, M., Kobayashi, Y., Narazaki, R. and Ohwaki, T. (2010) A new method for evaluating the bitterness of medicines in development using a taste sensor and a disintegration testing apparatus. Chem. Pharm. Bull. (Tokyo) **58**, 1009–1014.
48) Oohira, K. and Toko, K. (1996) Theory of electric characteristics of lipid/PVC/DOPP membrane and PVC/DOPP membrane in response to taste stimuli. Biophys. Chem. **61**, 29–35.
49) Ohshima, H. and Mitsui, T. (1978) A theory of the effects of calcium ions on the lamellar phase of dipalmitoyl lecithin. J. Colloid Interface Sci. **63**, 525–537.
50) Träuble, H., Teubner, M., Woolley, P. and Eibl, H. (1976) Electrostatic interactions at charged lipid membranes: I. Effects of pH and univalent cations on membrane structure. Biophys. Chem. **4**, 319–342.
51) Toko, K. and Yamafuji, K. (1981) Stabilization effect of protons and divalent cations on membrane structures of lipids. Biophys. Chem. **14**, 11–23.
52) Pungor, E. and Tóth, K. (1987) Ion selective electrodes: A review. Anal. Sci. **3**, 387–393.
53) Yoshida, Y., Matsui, M., Maeda, K. and Kihara, S. (1998) Physicochemical understanding of the selectivity at an ion selective electrode of the liquid membrane type and relation between the selectivity and distribution ratios in the ion-pair extraction. Anal. Chim. Acta **374**, 269–281.
54) Iiyama, S., Azuma, Y., Nagaishi, M. and Toko, K. (1996) Change in electric characteristics of membranes in response to taste stimuli with increasing amount of lipids in membrane matrix of PVC and plasticizer. Biophys. Chem. **61**, 23–27.
55) Nakatani, F., Ienaga, T., Wu, X., Tahara, Y., Ikezaki, H., Sano, H. *et al.* (2019) Development of a sensor with a lipid/polymer membrane comprising Na^+ ionophores to evaluate the saltiness enhancement effect. Sensors (Basel) **19**, 5251.
56) Xiang, Z., Jing, Y., Ikezaki, H. and Toko, K. (2021) Electrical properties of two types of membrane component used in taste sensors. Sensors (Basel) **21**, 8343.
57) Chen, K.M., Keri, D. and Barth, P. (2020) Computational design of G protein-coupled receptor allosteric signal transductions. Nat. Chem. Biol. **16**, 77–86.
58) Zhang, F., Klebansky, B., Fine, R.M., Xu, H., Pronin, A., Liu, H. *et al.* (2008) Molecular mechanism for the umami taste synergism. Proc. Natl. Acad. Sci. U.S.A. **105**, 20930–20934.
59) Sanematsu, K., Yamamoto, M., Nagasato, Y., Kawabata, Y., Watanabe, Y., Iwata, S. *et al.* (2023) Prediction of dynamic allostery for the transmembrane domain of the sweet taste receptor subunit, TAS1R3. Commun. Biol. **6**, 340.
60) Yoshimatsu, J., Toko, K., Tahara, Y., Ishida, M., Habara, M., Ikezaki, H. *et al.* (2020) Development of taste sensor to detect non-charged bitter substances. Sensors (Basel) **20**, 3455.
61) Ishida, M., Ide, H., Arima, K., Zhao, Z., Matsui, T. and Toko, K. (2022) Identification of the principle of taste sensors to detect non-charged bitter substances by ^{1}H-NMR measurement. Sensors (Basel) **22**, 2592.
62) Zhao, Z., Ishida, M., Onodera, T. and Toko, K. (2022) Effect of hydroxybenzoic acids on caffeine detection using taste sensor with lipid/polymer membranes. Sensors (Basel) **22**, 1607.
63) Xu, H., Zhao, Z., Kimura, S., Onodera, T. and Toko, K. (2023) Molecular structure underlying the allosteric mechanism of caffeine detection in taste sensor. Chemosensors **11**, 97.
64) Dunn, G.E. and Kung, F. (1966) Effect of intramolecular hydrogen bonding on ionization constants of substituted salicylic acids. Can. J. Chem. **44**, 1261–1269.
65) Nagy, P.I. (2014) Competing intramolecular vs.

intermolecular hydrogen bonds in solution. Int. J. Mol. Sci. **15**, 19562–19633.
66) Liao, X., Gautam, M., Grill, A. and Zhu, H.J. (2010) Effect of position isomerism on the formation and physicochemical properties of pharmaceutical cocrystals. J. Pharm. Sci. **99**, 246–254.
67) Bucar, D.-K., Henry, R.F., Lou, X., Duerst, R.W., MacGillivray, L.R. and Zhang, G.G.Z. (2009) Cocrystals of caffeine and hydroxybenzoic acids composed of multiple supramolecular heterosynthons: Screening via solution-mediated phase transformation and structural characterization. Cryst. Growth Des. **9**, 1932–1943.
68) Ishiwaki, T. (2013) Application of taste sensor to blending of coffee. *In* Biochemical Sensors: Mimicking Gustatory and Olfactory Senses (ed. Toko, K.). Pan Stanford Publishing, Singapore, pp. 83–90.
69) Wu, X., Miyake, K., Tahara, Y., Fujimoto, H., Iwai, K., Narita, Y. *et al.* (2020) Quantification of bitterness of coffee in the presence of high-potency sweeteners using taste sensors. Sens. Actuators B Chem. **309**, 127784.
70) Fujimoto, H., Narita, Y., Iwai, K., Hanzawa, T., Kobayashi, T., Kakiuchi, M. *et al.* (2021) Bitterness compounds in coffee brew measured by analytical instruments and taste sensing system. Food Chem. **342**, 128228.
71) Fukunaga, T., Toko, K., Mori, S., Nakabayashi, Y. and Kanda, M. (1996) Quantification of taste of coffee using sensor with global selectivity. Sens. Mater. **8**, 47–56.
72) Hayashi, N., Chen, R., Ikezaki, H., Yamaguchi, S., Maruyama, D., Yamaguchi, Y. *et al.* (2006) Techniques for universal evaluation of astringency of green tea infusion by the use of a taste sensor system. Biosci. Biotechnol. Biochem. **70**, 626–631.
73) Hayashi, N., Chen, R., Ikezaki, H. and Ujihara, T. (2008) Evaluation of the umami taste intensity of green tea by a taste sensor. J. Agric. Food Chem. **56**, 7384–7387.
74) Ujihara, T., Hayashi, N. and Ikezaki, H. (2013) Objective evaluation of astringent and umami taste intensities of matcha using a taste sensor system. Food Sci. Technol. Res. **19**, 1099–1105.
75) Cui, S., Wang, J., Geng, L., Wei, Z. and Tian, X. (2013) Determination of ginseng with different ages using a taste-sensing system. Sens. Mater. **25**, 241–255.
76) Uchiyama, Y., Yamashita, M., Kato, M., Suzuki, T., Omori, M. and Chen, R. (2011) Evaluation of the taste of tea with different degrees of fermentation using a taste sensing system. Sens. Mater. **23**, 501–506.
77) Toko, K. and Tahara, Y. (2016) Beer analysis using an electronic tongue. *In* Electronic Noses and Tongues in Food Science (ed. Mendez, M.L.R.) Academic Press, Cambridge, pp. 161–170.
78) Zhang, H., Zou, G., Liu, W. and Zhou, Z. (2020) Beer taste detection based on electronic tongue. Sens. Mater. **32**, 2949–2958.
79) Liu, J., Yang, J., Wang, W., Fu, S., Shi, Y. and Men, H. (2016) Automatic evaluation of sensory information for beer at a fuzzy level using electronic tongue and electronic nose. Sens. Mater. **28**, 785–795.
80) Iiyama, S., Suzuki, Y., Ezaki, S., Arikawa, Y. and Toko, K. (1996) Objective scaling of taste of sake using taste sensor and glucose sensor. Mater. Sci. Eng. C **4**, 45–49.
81) Totsuka, A. (2013) Application of multichannel taste sensor for winemaking. *In* Biochemical Sensors: Mimicking Gustatory and Olfactory Senses (ed. Toko, K.). Pan Stanford Publishing, Singapore, pp. 103–116.
82) Iiyama, S., Yahiro, M. and Toko, K. (1995) Quantitative sensing of mineral water with multichannel taste sensor. Sens. Mater. **7**, 191–201.
83) Hayashi, N., Ujihara, T., Hayakawa, F., Nakano, Y., Kawakami, T. and Ikezaki, H. (2020) Standardization of tomato juice tastes using a taste sensor approach. Biosci. Biotechnol. Biochem. **84**, 2569–2575.
84) Toko, K., Iyota, T., Mizota, Y., Matsuno, T., Yoshioka, T., Doi, T. *et al.* (1995) Heat effect on the taste of milk studied using a taste sensor. Jpn. J. Appl. Phys. **34**, 6287–6291.
85) Mizota, Y., Matsui, H., Ikeda, M., Ichihashi, N., Iwatsuki, K. and Toko, K. (2008) Flavor evaluation of UHT reconstituted milk processed by direct and indirect heat treatment using sensors. Sens. Mater. **20**, 243–253.
86) Yamada, H., Mizota, Y., Toko, K. and Doi, T. (1997) Highly sensitive discrimination of taste of milk with homogenization treatment using taste sensor. Mater. Sci. Eng. C **5**, 41–45.
87) Iiyama, S., Yahiro, M. and Toko, K. (2000) Measurements of soy sauce using taste sensor. Sens. Actuators B Chem. **66**, 205–206.
88) Akitomi, H., Tahara, Y., Yasuura, M., Kobayashi, Y., Ikezaki, H. and Toko, K. (2013) Quantification of tastes of amino acids using taste sensors. Sens. Actuators B Chem. **179**, 276–281.
89) Terashita, K. and Wakabayashi, O. (2013) Quality engineering approach to bitterness-masked formulations and establishment of bitterness masking evaluation system using taste-sensing system. *In* Biochemical Sensors: Mimicking Gustatory and Olfactory Senses (ed. Toko, K.). Pan Stanford Publishing, Singapore, pp. 231–249.
90) Uchida, T., Yoshida, M., Hazekawa, M., Haraguchi, T., Furuno, H., Teraoka, M. *et al.* (2013) Evaluation of palatability of 10 commercial amlodipine orally disintegrating tablets by gustatory sensation testing, OD-mate as a new disintegration apparatus and the artificial taste sensor. J. Pharm. Pharmacol. **65**, 1312–1320.
91) Woertz, K., Pein, M. and Breitkreutz, J. (2013) Development and characterization of medicines for children. *In* Biochemical Sensors: Mimicking Gustatory and Olfactory Senses (ed. Toko, K.). Pan Stanford Publishing, Singapore, pp. 185–203.
92) Liu, R.X., Gao, X.J., Wang, J.M., Dai, L.P., Kang, B.Y., Zhang, L. *et al.* (2017) Traditional human

taste panel and taste sensors methods for bitter taste masking research on combined bitterness suppressants of berberine hydrochloride. Sens. Mater. **29**, 105–116.
93) Takagi, S., Toko, K., Wada, K. and Ohki, T. (2001) Quantification of suppression of bitterness using an electronic tongue. J. Pharm. Sci. **90**, 2042–2048.
94) Yasuura, M., Shen, Q., Tahara, Y., Yatabe, R. and Toko, K. (2015) Development and investigation of a sweetness sensor for sugars − Effect of lipids. Sens. Mater. **27**, 351–358.
95) Ye, Z., Ai, T., Wu, X., Onodera, T., Ikezaki, H. and Toko, K. (2022) Elucidation of response mechanism of a potentiometric sweetness sensor with a lipid/polymer membrane for uncharged sweeteners. Chemosensors **10**, 166.
96) Toyota, K., Cui, H., Abe, K., Habara, M., Toko, K. and Ikezaki, H. (2011) Sweetness sensor with lipid/polymer membranes: response to various sugars. Sens. Mater. **23**, 475–482.
97) Toyota, K., Cui, H., Abe, K., Habara, M., Toko, K. and Ikezaki, H. (2011) Sweetness sensor with lipid/polymer membranes: sweet-responsive substances. Sens. Mater. **23**, 465–474.

(Received Jan. 25, 2023; accepted May 1, 2023)

Profile

Dr. Kiyoshi Toko is a University Professor at the Institute for Advanced Study, and a Professor at the R&D Center for Five-Sense Devices, Kyushu University. He proposed a concept "to measure taste" around 30 years ago and succeeded in developing taste sensors using lipid membranes, *i.e.*, the electronic tongue. At present, this taste sensor is sold commercially by Intelligent Sensor Technology, Inc. (INSENT) and used by food and pharmaceutical companies around the world. Two companies, INSENT and Taste & Aroma Strategic Research Institute Co., Ltd., were established based on his research. In addition, he is now developing a multi-array odor sensor (e-nose) in cooperation with Panasonic. He has directed and continues to be involved in several government-funded projects in food, nanotechnology, and integrated sensing technology using biosensors and the taste/odor sensor. As a result of these accomplishments, he has won numerous prizes such as the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (MEXT) and the Medal with Purple Ribbon. His research results are frequently covered on TV programs.