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Research Progress on Biomimetic Taste Sensors for Food and Pharmaceutical Detection

Jingyun Liu

School of Food and Biological Engineering, Hefei University of Technology, Hefei, China
1051147899@qq.com

Abstract. Taste perception is a core physiological function of organisms for recognizing exogenous chemical substances. With the advantages of high sensitivity, high specificity, rapid response and good standardizability, biomimetic taste sensors have important application value in fields including food safety detection, drug screening, environmental pollutant monitoring and clinical nutritional assessment. This paper systematically summarizes the research status of biomimetic sensing technologies targeting five basic tastes: bitter, sweet, sour, umami and salty. Focusing on technical routes such as biological organoid-on-a-chip, living cell electrophysiological sensing, purely chemical/optical sensing, and receptor-functionalized electrochemical/nanochannel sensing, this paper concludes the recognition mechanisms, material systems, device fabrication and detection performances of different taste sensors, and compares their linear ranges, limits of detection, response characteristics and applicable scenarios. This work emphatically analyzes the breakthroughs of representative technologies including taste organoid-on-a-chip, cardiomyocyte-based bioelectronic tongue, dual photoresponsive devices based on hydrogen-bonded organic frameworks, graphene field-effect transistors and biomimetic ionic nanochannels. The current challenges of biomimetic taste sensors in terms of stability, selectivity and adaptability to complex matrices are summarized, and the development trends of multimodal integration, intellectualization, miniaturization and compatibility for both *in vivo* and *in vitro* use are prospected. This study provides a reference for the research and development of new-generation biomimetic taste sensing systems.

Keywords: Biomimetic Taste Sensors, Electronic Tongue, Taste Receptors, Organoid-on-a-Chip, Food and Pharmaceutical Detection

1. Introduction

Taste is an essential chemosensory system for mammals to perceive external chemical signals, avoid risks and intake nutrients. Bitter taste warns organisms of toxic and harmful substances, sweet taste indicates energy sources, sour taste judges food freshness, umami taste evaluates nutritional quality, and salty taste regulates the electrolyte balance of the body. The five basic tastes work together to form a chemical defense and intake regulation network for organisms. Traditional taste evaluation relies on human sensory panel assessment, which has obvious drawbacks such as strong subjectivity, poor repeatability, difficulty in quantification and lack of standardization. Conventional instrumental

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analysis methods including chromatography and mass spectrometry can realize accurate quantification of target substances, but they fail to reproduce the real processes of receptor recognition, signal transduction and neural coding in living organisms, and cannot reflect biological taste responses equivalently.

With the rapid integration of bioelectronics, nanomaterials science, organoid technology and micro-nano processing technology, taste sensors have achieved vigorous development. By simulating the biological taste recognition mechanism, these sensors can realize specific identification, high-sensitivity quantification and real-time dynamic monitoring of taste substances. In recent years, researchers have constructed biomimetic sensing interfaces at multiple levels including molecular receptors, living cells, organoids and neural circuits. Combined with signal conversion modes such as electrochemistry, optics, electrophysiology and ion channel regulation, a series of sensing devices for bitter, sweet, sour, umami and salty substances have been developed. Continuous breakthroughs have been made in key indicators such as limit of detection, linear range, selectivity and response speed, and these devices have been gradually applied to food flavor evaluation, drug bitterness screening, environmental toxicant detection, clinical blood glucose/sodium ion monitoring and other scenarios.

At present, biomimetic taste sensing has formed three major technical branches: biological type, chemical type and bio-chemical hybrid type. Each technical route has its own advantages and disadvantages in recognition mechanism, material system, detection performance and application adaptability. Nevertheless, existing sensors still face bottlenecks such as interference from complex matrices, insufficient long-term stability, cross-talk among multiple taste signals and poor consistency between *in vivo* and *in vitro* responses. It is urgent to systematically sort out research progress, clarify technical gaps and point out future development directions. Based on the latest research achievements, this paper comprehensively reviews the construction strategies, recognition mechanisms, performance parameters and application status of biomimetic sensors for five basic tastes, analyzes key technical challenges, and prospects future development trends, so as to provide a systematic reference for research and application in the field of biomimetic taste sensing (Figure 1).

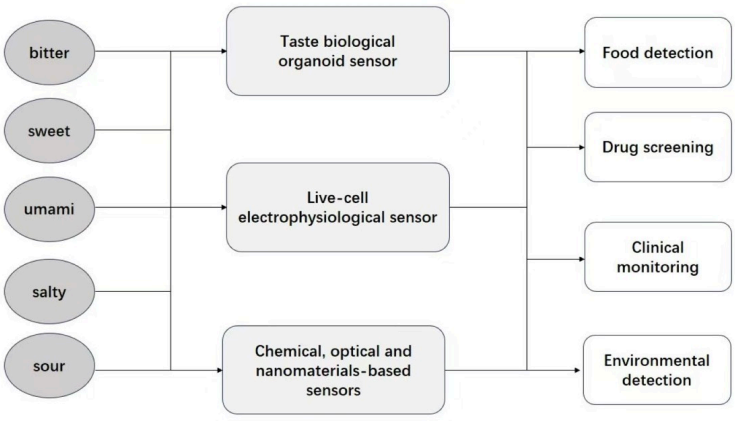

Figure 1. Graphical abstract

2. Bitter taste sensors

As an important perception system for human beings, bitter taste has a wide range of application values in food safety monitoring, drug screening and environmental pollutant detection. In recent

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years, driven by the rapid development of bioelectronics and nanotechnology, researchers have developed various novel biomimetic taste sensing systems to realize the specific identification and high-sensitivity detection of bitter substances [1]. This section discusses the current research status and development trends of biomimetic taste sensing technologies from three aspects: biological organoid-on-a-chip, living cell electrophysiological sensing and purely chemical & optical sensing.

Jianguo Wu and colleagues established a Taste Organoids-on-a-Chip System (TOS). This system couples mouse-derived taste organoids with platinum black microelectrode arrays (MEA), and realizes taste perception by real-time recording of changes in extracellular field potentials. The limit of detection of this system for phenylthiocarbamide (PTC) reaches 0.001 mM. Obvious signal changes can be observed when the concentration of PTC is 0.1 mM, and the system can effectively identify concentration gradients. Principal component analysis is adopted to distinguish bitter stimuli with different concentrations [2].

The research team led by Xinwei Wei innovatively used rat cardiomyocytes as taste sensing elements and constructed the first *in vitro* bioelectronic tongue (BioET) based on cardiomyocytes and microelectrode arrays. Rats possess 37 functional TAS2R genes, among which *Tas2r108*, *Tas2r126*, *Tas2r135*, *Tas2r137* and *Tas2r143* show the highest expression levels [3]. Relevant studies have verified that endogenous bitter taste receptors Tas2r135, Tas2r108 and Tas2r137 are expressed in cardiomyocytes of Sprague-Dawley (SD) rats. When bitter compounds such as denatonium (Dena) and diphenidol (Diph) bind to receptors on the cardiomyocyte surface, the G protein-coupled receptor signaling pathway is activated, causing cell membrane depolarization and changes in ion channel activity. These changes further lead to specific variations in extracellular field potential amplitude (FPA) and firing rate (FR). In quantitative detection, the normalized FPA shows a good linear relationship with the concentration of bitter compounds. The linear equation for Dena (activating Tas2r135) is $Y = -0.2878X + 1.144$ ($R^2 = 0.9846$), with a limit of detection of 3.46×10^{-6} M. The linear equation for Diph (activating Tas2r108 and Tas2r137) is $Y = -0.3133X + 1.136$ ($R^2 = 0.9887$), with a limit of detection of 2.92×10^{-6} M [4].

Zishuo Zhang's group developed an intelligent multi-photoresponsive artificial tongue named Tb@MCATMA (abbreviated as Tb@1) based on Tb^{3+}-functionalized hydrogen-bonded organic frameworks (HOF). This system realizes synchronous identification of bitter substances via dual signal mechanisms of fluorescence and room-temperature phosphorescence. It presents sensitive responses to two bitter substances, 2-furfural (2-FA) and 5-hydroxymethylfurfural (5-HMF). The fluorescence emission intensity at 544 nm decreases with the increase of bitter substance concentration, showing a favorable linear correlation. The linear equation for 2-FA is $I_{544} = -12402.2\log c(\text{2-FA}) - 39217.7$ ($R^2 = 0.988$), and the linear equation for 5-HMF is $I_{544} = -13732.5\log c(\text{5-HMF}) - 43322.7$ ($R^2 = 0.996$). Their limits of detection are 5.89×10^{-7} M and 2.82×10^{-7} M respectively [5]. In practical application, the team of Renato Luiz Faraco Filho adopted a Mach–Zehnder interferometer (MZI) composed of two long-period fiber gratings (LPFGs) to build a novel optical fiber refractive index sensor, which can detect the International Bitterness Units (IBU) caused by iso-α-acids in beer. For beer samples with IBU values ranging from approximately 7 to 13, the repeatability error of this sensor is 0.17±0.09 IBU (upper limit: 0.4 IBU), and the reproducibility is 0.30±0.08 IBU (upper limit: 0.57 IBU) [6]. F. Gokbel's team synthesized a novel dual-response fluorescent chemical sensor FZ-3 with a hemicyanine structure through condensation reaction between 2,3,3-trimethyl-1-propyl-3H-indol-1-ium iodide and 3-chloronicotinaldehyde. Within the physiological pH range of 3.9–8.0, this sensor exhibits a turn-on fluorescence response toward CN^- at 414 nm with a limit of detection of 1.08 μM, and a turn-on fluorescence response toward histidine (His) at 463 nm with a limit of detection of 2.80 μM [7].

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3. Sweet taste sensors

As one of the core functions of the mammalian chemosensory system, sweet taste perception plays an increasingly important role in nutrient intake, energy metabolism regulation and the occurrence of metabolic diseases. At present, research on biomimetic sensing for sweet taste detection is mainly carried out at the levels of molecular receptors, organoids and neural circuits. Technologies at different levels complement and cooperate with each other, forming an *in vitro* research system for sweet taste perception.

At the molecular receptor level, biomimetic electrochemical sensors based on conformational changes of human sweet taste receptor T1R2 represent an important breakthrough in high-sensitivity detection. Sweet taste receptors belong to Class C G protein-coupled receptors, which are formed by the heterodimerization of T1R2 and T1R3 subunits. The extracellular Venus flytrap (VFT) domain is the key region for recognizing sweet molecules. Jing Ye's team obtained T1R2 VFT protein via the *Escherichia coli* heterologous expression system, and modified glassy carbon electrodes with Ti_3C_2 MXene/gold nanoparticles (AuNPs) nanocomposites to construct a three-dimensional sensing interface. When sweet molecules such as sucrose, glucose and aspartame bind to the VFT domain, the receptor conformation changes from the "open" state to the "closed" state. The immuno-competitive mechanism driven by such conformational changes converts the weak signal generated by traditional small molecule-protein binding into a strong signal derived from protein-protein interaction. The linear detection range of this sensor for sucrose is 50 pM to 50 μM, with an extremely low limit of detection of 5.1 pM. The limits of detection for glucose and aspartame are 4.7 pM and 5.4 pM respectively [8]. The team of J.-Y. Jeong applied relevant technologies to sweet taste detection in complex food matrices such as apple juice and chamomile tea. They covalently immobilized target substances on the floating electrode surface of carbon nanotube field-effect transistors (CNT-FET) through cysteine linkers, and fabricated an ultra-sensitive artificial sweet taste bioelectronic tongue. The sensor presents a concentration-dependent response to diluted apple juice, with an initial response concentration of about 10^{-18} (v/v) and signal saturation at approximately 10^{-4} (v/v). Fitted by the Hill equation, the half maximal effective concentration (EC_{50}) is calculated as 1.00×10^{-10} (v/v). After adding sucrose (100 mg/mL) to chamomile tea and preparing serial dilutions, the sensor can effectively detect sucrose, with an EC_{50} of about 1.89×10^{-8}, which is in the same order of magnitude as the results obtained in buffer solution and apple juice [9].

Taste bud organoids have the advantages of easy acquisition, strong activity and high similarity to *in vivo* taste buds, providing an alternative and convenient method for studying taste functions and potential mechanisms [10]. Jianguo Wu's group also adopted the Taste Organoids-on-a-Chip System (TOS), which combines mouse-derived taste organoids with platinum black microelectrode arrays (MEA). Sweet taste perception is realized by real-time monitoring of extracellular field potential changes, and the detection threshold of this system for sucrose is about 0.125–0.25 g/mL [2].

Chunlian Qin's team cultured primary hypothalamic neurons on the surface of MEA chips. Immunofluorescence staining verified the coexistence of neurons (TuJ1-positive) and astrocytes (GFAP-positive), and confirmed the functional expression of sweet taste receptors. Three types of neurons were identified: glucose-excited neurons whose firing frequency increases with the rise of glucose concentration within the range of 0.4–6 mM, glucose-inhibited neurons whose firing frequency decreases with increasing glucose concentration within 1–8 mM with a half maximal inhibitory concentration (IC_{50}) of 4.18 mM, and non-glucose-sensitive neurons. The limit of detection of this system for glucose is as low as 0.01 mM, covering the physiological and pathological concentration range from hypoglycemia (0.2 mM) to hyperglycemia (4.5 mM) [11].

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4. Sour taste sensors

The recognition of sour taste acts as a vital defense mechanism of the mammalian taste system, which helps to identify unripe, fermented or spoiled food. Different from bitter and sweet tastes mediated by G protein-coupled receptors, sour taste perception is mainly regulated by the OTOP1 ion channel, which is specifically expressed in type III taste receptor cells [12]. When acidic substances enter cells, cytoplasmic acidification occurs and leak potassium channels are blocked, resulting in cell membrane depolarization and the generation of action potentials.

Jianguo Wu's team co-cultured taste stem cell-derived organoids with microelectrode arrays (MEA) for 14 days. The obtained taste organoids can maintain high expression of OTOP1, and type III cells on the chip keep high activity (over 90%) for more than 7 days. When stimulated by acetic acid, the TOS system realizes sour taste identification by recording changes in the power spectral density (PSD) of extracellular field potentials, with a detection threshold of 1.56 mg/mL [2].

Ziyu Liang's group adopted multiple research methods including knockout mouse models, patch-clamp electrophysiological recording, heterologous expression system (HEK-293 cells) and behavioral tests to construct an ammonium chloride taste sensor based on the proton channel OTOP1. OTOP1 can serve as an effective sensing element for ammonium chloride detection. In HEK-293 cells expressing mouse OTOP1 (mOTOP1), human OTOP1 and variants from other species, extracellular NH_4Cl can induce dose-dependent inward currents, with a half maximal effective concentration of 18.66 mM and a detectable concentration range of 1–160 mM. In isolated type III taste receptor cells, ammonium chloride at a concentration as low as 5 mM can trigger action potentials. Behavioral experiments further verified that this channel participates in the perception of ammonium chloride taste within the concentration range of 100–500 mM [13].

Zishuo Zhang's team developed Tb^{3+}-functionalized hydrogen-bonded organic framework sensors, which achieve accurate identification of citric acid and oxalic acid via dual-mode response of fluorescence and phosphorescence. The material takes melamine-cyanuric acid (MCA) hydrogen-bonded framework as the main body, incorporates trimesic acid (TMA) and coordinates with Tb^{3+}, producing green fluorescence of Tb^{3+} (544 nm) and dark blue phosphorescence of TMA (410 nm) simultaneously. By adjusting the excitation wavelength (262 nm and 290 nm), the characteristic photoresponses of citric acid and oxalic acid can be distinguished. The limits of detection for citric acid and oxalic acid are 1.06×10^{-6} M and 5.61×10^{-7} M respectively [5]. To further improve the recognition ability toward sour substances, the research group introduced europium ion (Eu^{3+}) into the melamine-cyanuric acid hydrogen-bonded framework (HOF MCA) to identify four organic acids: citric acid, oxalic acid, malic acid and fumaric acid. The detection principle remains the same. The corresponding limits of detection are as follows: citric acid 7.00×10^{-7} M / 5.53×10^{-7} M, oxalic acid 6.58×10^{-7} M / 5.98×10^{-7} M, malic acid 2.65×10^{-7} M / 3.09×10^{-7} M, and fumaric acid 5.91×10^{-7} M / 6.54×10^{-7} M [14].

5. Umami and salty taste sensors

Umami and salty tastes present synergistic effects. Umami taste is triggered by amino acids such as glutamic acid and nucleotide substances through activating specific G protein-coupled receptors, and it is a core index for food flavor evaluation. Traditional sensory evaluation relies on professional tasting panels, which is subject to strong subjectivity and poor standardization. Although conventional instrumental analysis techniques such as high-performance liquid chromatography coupled with mass spectrometry can provide objective data, they cannot simulate the receptor recognition and signal transduction processes of the biological taste system, and thus fail to reflect

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real sensory experience [15]. Salty taste is closely related to human health. The per capita sodium intake worldwide generally exceeds the standard. Excessive sodium intake easily causes cardiovascular diseases, stroke and renal dysfunction, while insufficient intake may lead to hyponatremia [16]. Therefore, the development of high-selectivity and high-sensitivity detection technologies for salty substances is of great significance for quality control in the food industry and clinical nutrition monitoring.

The research and development of umami peptides is a hot topic in food flavoring research [17]. Yanyang Yu's group adopted a sensing strategy based on purified receptor proteins, taking the Venus flytrap (VFT) domain of T1R1/T1R3 heterodimer as the core recognition element, and realized quantitative analysis of umami substances by means of bio-layer interferometry (BLI) and electrochemical detection (Figure 2). The team acquired T1R1-VFT protein via the *Escherichia coli* heterologous expression system, covalently immobilized umami peptides on the surface of AR2G sensor probes, and monitored the binding-dissociation kinetic processes between receptors and ligands in real time using BLI technology. Relevant literature indicates that when two umami peptides bind to T1R1-VFT simultaneously, the binding free energy decreases significantly from −7.3 kcal/mol for single ligand binding to −11.19 kcal/mol, and the kinetic equilibrium constant drops from 1.2×10^{-6} M to 8.3×10^{-7} M, which means a remarkable increase in binding affinity. This finding reveals the mechanism of umami synergistic effect at the molecular level [18]. Based on the taste sensing technology with artificial lipid membrane potential response [19], Jianan Zhang's group used the TS-5000Z taste sensing system to build an umami taste sensor equipped with lipid membranes, which can quantitatively detect typical umami substances and novel umami compounds including umami peptide Ser-Phe-Glu. Within specific concentration ranges, the detectable concentration range is 0–75 mM for monosodium glutamate (MSG), 0.01–50 mM for sodium aspartate, 0–75 mM for Fru-Glu, 0.01–10 mM for disodium succinate, 0–25 mM for umami peptide Ser-Phe-Glu, and 0.5–10 mM for both IMP and GMP [20]. Mingyang Li's team fabricated asymmetric conical nanochannels on PET substrates by ion track etching technology. The Venus flytrap domain of human umami receptor T1R1 (T1R1-VFT) was covalently immobilized on the inner wall of nanochannels via amidation reaction, constructing T1R1-VFT functionalized biomimetic ionic nanochannel sensors. The specific binding between T1R1-VFT and umami ligands induces surface charge redistribution and local conformational changes of proteins, which modulates transmembrane ionic currents and further realizes the recognition and detection of umami substances (Figure 2). This sensor can detect four typical umami substances including IMP, MSG, WSA and umami peptide BMP, with a linear detection range of 1 pM to 10 μM. The limits of detection are 0.75 pM for IMP, 0.76 pM for MSG, 0.59 pM for WSA and 0.12 pM for BMP respectively [21].

Compared with other taste sensors, researches on salty taste sensors are relatively limited. The solution-gated field-effect transistor based on Nafion/calixarene/graphene proposed by Chung Won Lee's team represents a typical technical route driven by material chemistry. This sensor adopts single-layer graphene prepared by chemical vapor deposition (CVD) as the channel, calixarene is coated as the specific receptor for Na^+, and Nafion film is spin-coated as a molecular sieve to allow only small cations to penetrate. Combined with PDMS microfluidic channels, automatic detection is achieved. The τ_{90} response time is only 33 seconds, the sensitivity reaches 1.20936 mM^{-1}, the detection range is 100 nM to 10 mM, and the service life of the device is up to 220 days [22]. The Taste Organoids-on-a-Chip System (TOS) developed by Jianguo Wu's team can distinguish five concentration gradients of NaCl solution ranging from 6 M to 0.75 M, with a detection threshold of 1.5 M [2].

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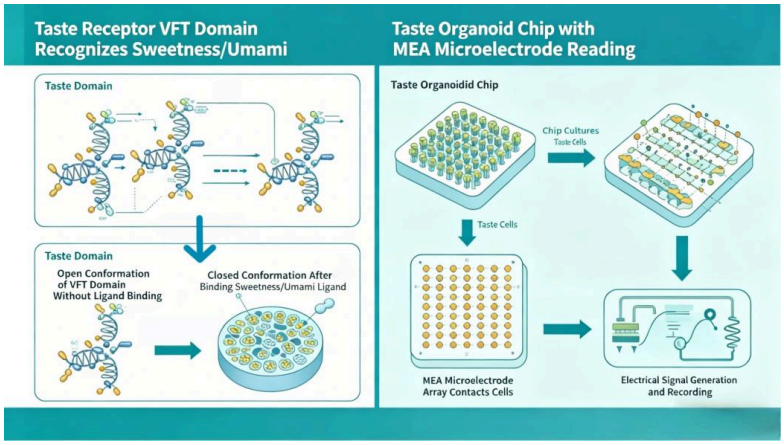

Figure 2. Sweet/umami recognition mediated by VFT domain and detection system of taste organoid chip equipped with MEA microelectrode array

6. Conclusions and prospects

This paper systematically reviews the research progress of biomimetic sensing technologies for five basic tastes: bitter, sweet, sour, umami and salty. Focusing on mainstream technical routes including biological organoid-on-a-chip, living cell electrophysiological sensing, purely chemical & optical sensing, receptor-functionalized electrochemical sensing and nanochannel sensing, the recognition mechanisms, device fabrication strategies and detection performance characteristics of various taste sensors are elaborated in depth. Research results show that relying on interdisciplinary technologies such as nanomaterials, organoid culture, microelectrode arrays, genetic engineering and micro-nano processing, current biomimetic taste sensors have realized specific identification and high-sensitivity quantitative detection of various taste substances. Significant breakthroughs have been made in key indicators including limit of detection, linear range, response speed and signal stability, and these sensors can be well applied to multiple scenarios such as food safety monitoring, drug bitterness screening, food flavor evaluation, clinical nutrition and electrolyte monitoring, as well as environmental pollutant identification. Among these devices, taste organoid chips can highly simulate *in vivo* real taste responses and support synchronous perception of multiple tastes. Living cell-based bioelectronic tongues using cardiomyocytes and neurons feature simple preparation and excellent linear relationships. Chemical and optical devices such as hydrogen-bonded organic frameworks and fluorescent probes as well as fiber grating sensors possess outstanding stability and portability, with limits of detection reaching the order of 10^{-7} M. Nano-composite materials and biomimetic ionic nanochannel sensors based on the VFT domain of taste receptors achieve ultra-high sensitivity at the femtomole level, showing remarkable advantages in the analysis of trace sweet and umami substances. Although the existing biomimetic taste sensing technologies have formed a multi-dimensional research system covering molecular, cellular, organoid and neural circuit levels, there are still challenges in anti-interference capability against complex food matrices, long-term device stability, suppression of multi-taste signal cross-talk, response consistency between *in vivo* and *in vitro* conditions, standardized fabrication and industrial application.

In the future, with the continuous integration of intelligent algorithms, flexible electronics, wearable devices and biocompatible packaging technologies, biomimetic taste sensors will develop toward multimodal integration, full taste profile detection by single device, miniaturization, portability and dynamic *in vivo* monitoring for clinical use (Figure 3). These sensors will gradually achieve large-scale application from basic laboratory research to the food industry, pharmaceutical

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research and development, clinical detection and other fields, and become core supporting technologies in the field of intelligent chemical perception and precise detection.

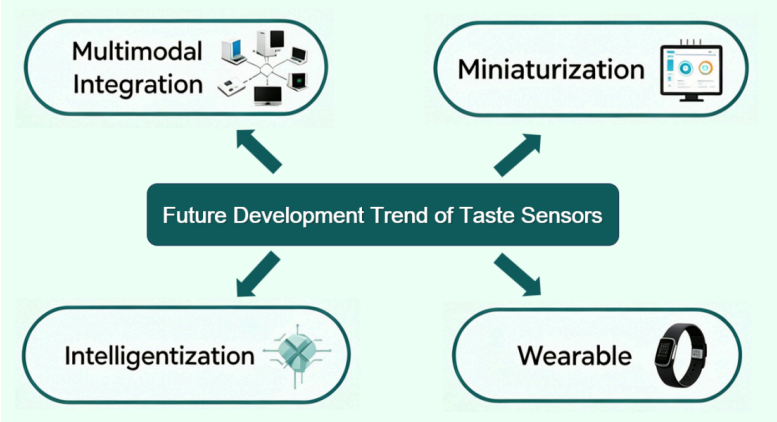

Figure 3. Future development trends of biomimetic taste sensing systems: Multimodal Integration, Miniaturization, Wearable and Intelligentization

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