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Emerging Intraoral Biosensors

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Abstract: Biomedical devices that involved continuous and real-time health care monitoring have drawn much attention in modern medicine, of which skin electronics and implantable devices are widely investigated. Skin electronics are characterized for their non-invasive access to the physiological signals, and implantable devices are superior at the diagnosis and therapy integration. Despite the significant progress achieved, many gaps remain to be explored to provide a more comprehensive overview of human health. As the connecting point of the outer environment and human systems, oral cavity contains many unique biomarkers that are absent from skin or inner organs, could become a promising alternative locus for designing health care monitoring devices. In this review, we outline the status of oral cavity during the communication of the environment and human systems and compare the intraoral devices with skin electronics and implantable devices from the biophysical and biochemical aspects. We further summarize the established diagnosis database and technologies that could be adopted to design intraoral biosensors. Finally, the challenges and potential opportunities for intraoral biosensors are discussed. Intraoral biosensors could become an important complement for existing biomedical devices to constitute a more reliable health care monitoring system.

1. Introduction

The development and integration of materials science, soft electronics, sensing techniques, and information technologies have greatly propelled the evolution of medical science.[1, 2] Consequently, biomedical devices that involved continuous and real-time health care monitoring have emerged and drawn great attention. These devices could collect multi-modal, whole-body physiological and mental information to the digital world to provide an integral and comprehensive overview of human health, and thus greatly enhance the diagnosis accuracy and therapy output.[3-5]

Among various health care monitoring entities, skin electronics and implantable devices have been widely investigated due to their unique status and virtues. Skin electronics are characterized for their non-invasive access, large-area implementation, wear and comfort capability. Many conformable and stretchable skin electronics have been developed, which could detect reliable biophysical and environmental signals that are related to human health.[6, 7] Implantable devices can integrate complex monitoring, analysis and therapy processes, and free the patients from the tedious hospital diagnosis and treatment.[8] Despite the advantageous performances for these biomedical devices, many challenges remain to be settled: limited biochemical signals for skin electronics and invasive issues for implantable devices.[9, 10] As a result, new medical devices that accommodated by other body sites can be designed to supplement these gaps.

Oral cavity as the connecting point of outer environment and human systems, could be a promising locus for designing health care monitoring devices. It is the starting point of the digestive system and respiratory system, undertaking the main task for the matter exchange,[11-13] providing established protective systems against the invasion of bacteria.[14, 15] Meanwhile, oral cavity is also connected to circulatory and nervous systems, acting as an indicator for systemic diseases.[16, 17] Many reviews on oral cavity have focused on investigating

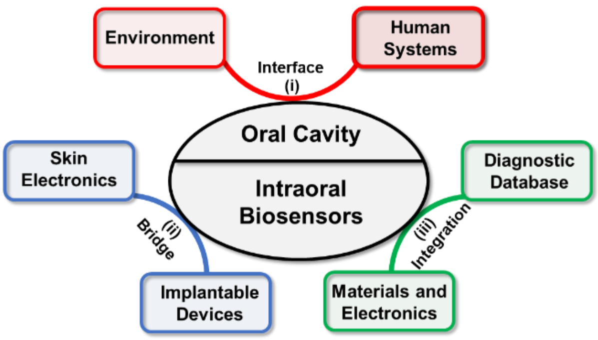

Figure 1. Status of oral cavity and intraoral biosensors: (i) Oral cavity acts as an important interface between environments and human systems. (ii) Many opportunities lie between the skin electronics and implantable devices, where intraoral biosensors can become a promising supplement. (iii) By integrating the high throughput biomarker screening information with the well-established material and electronics, plenty of intraoral biosensors can be designed for health care monitoring.

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the secretion, function, and compositions of saliva.[18-20] The saliva-based biomarkers were investigated by various methods, ranging from high-throughput screening methods to point of care (POC) diagnosis techniques.[21-23] These biomarkers and sensing methods could provide a foundation for the development of intraoral biosensors. With the incorporation of existing diagnostic databases and established biosensing techniques, intraoral biosensors could be developed into a distinctive member of the health care monitoring toolbox. In this tutorial review, we firstly introduce the role of oral cavity, emphasizing its importance as the interface of the environment and human systems (Figure 1-i, section 2). Subsequently, we explain the unique characters of intraoral biosensors compared with skin electronics and implantable devices (Figure 1-ii, section 3). The design strategies of intraoral biosensors from the aspects of diagnosis database, materials and electronics are introduced (Figure 1-iii, section 4). Lastly, the challenges and measures to be taken are discussed to accelerate the development of intraoral biosensors (Section 5).

2. Status of oral cavity

Oral cavity, ranging externally from lips and cheeks to the anterior pillars of the faucets, undertakes multiple important roles as the interface of environment and human systems.[24] Oral cavity serves as the connecting point of the outer environment, digestive system and respiratory system, initiating the nutrition intake and air exchange with the environment.[25] At the same time, the excretory system and immune system form a protective and defensive barrier to protect the human body from the invasion of pathogens and xenobiotics during matter exchange processes.[16, 18] Moreover, oral cavity is also connected to the circulatory system and innervated by the neuron system, which made the relative biomarkers promising indicators for human physical and mental state.[17]

2.1 Matter exchange between environment and human systems

As the starting point of the digestive system, oral cavity has established a coordinated nutrition intake system, combining mechanical and chemical digestive processes.[24] Many structures are involved in the food mastication process, ranging from the soft oral mucosa, tongues to the hard palate and teeth, which endow oral cavity the ability to accommodate food with various mechanical properties.[12] These well-defined soft and rigid structures can be utilized to accommodate intraoral biosensors. Moreover, oral cavity and oral fluids play important roles in the food intake processes, including surface coating and clustering, colloidal interaction, complexation, enzymatic breakdown and binding of aroma compounds for the taste and taste bud maintaining.[11, 26] Besides, due to the connectedness of the digestive systems, biomarkers from the inner part of the digestive systems can be utilized as biomarkers for health care monitoring.[27-29]
Oral cavity is also connected with nose acting as the origin of the respiratory systems, participating in the air exchanging processes. Many volatile organic compounds (VOCs, including hydrocarbons, alcohols, aldehydes, ketones, esters, and aromatic compounds, etc.) are involved in the metabolism processes of human body.[30, 31] Disease-related VOCs are produced due to abnormality of specific biochemical pathways in the body and are distributed through blood to the breath and other media. Disease-specific VOCs can be of great value for non-invasive diagnosis, they originate from the metabolic alterations due to the exogenous agents (exogenous VOCs, alcohol, smoking, etc.).[32]

2.2 Protective and defensive systems in oral cavity

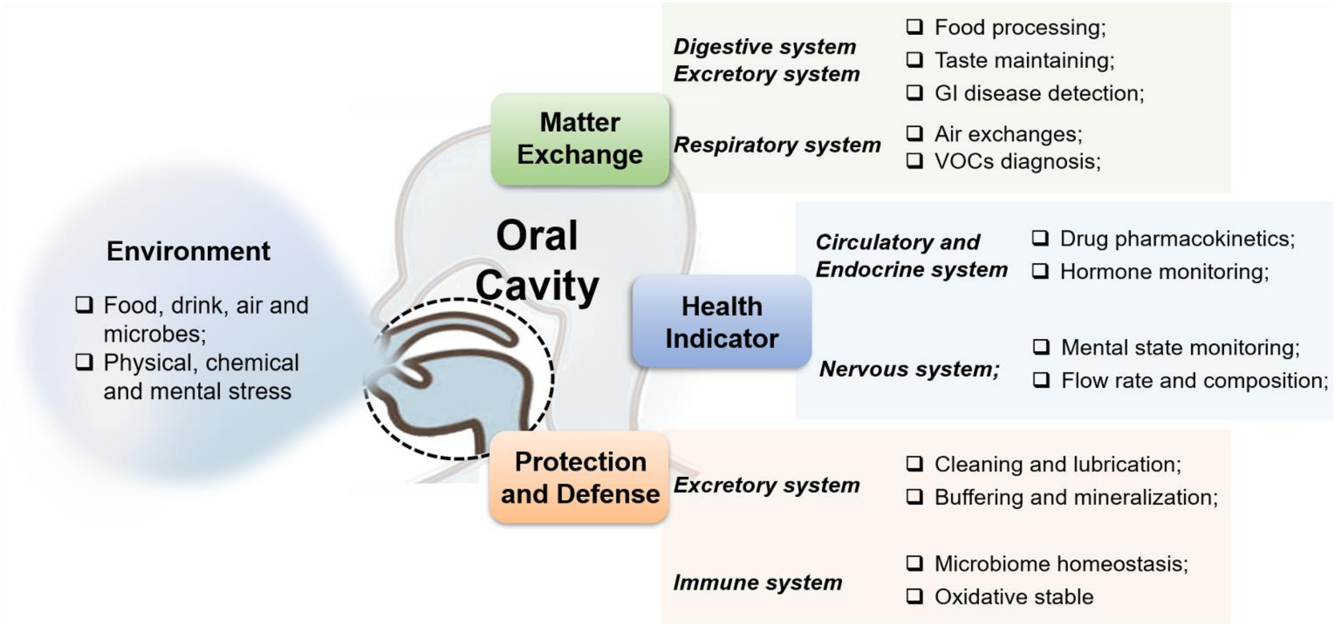

Figure 2. Oral cavity as the interface between environment and human systems.

Two protective systems are involved to protect the human body from the invasion of pathogens and xenobiotics from the environment. At first, excretory system (saliva) is necessary for the ingestion processes, providing coating molecules for the soft and hard tissues, as well as many other functions varied from the cleaning, buffering, lubrication and mineralization.[33-35] These functions are critical in the maintenance of stable and safe environment of oral cavity.[14]

The main task of immune system in oral cavity is to keep the homeostasis of microbes and prevent the oral cavity from the invasion of pathogens.[36] Dysbiosis of the oral bacteria can result in disease state in oral cavity, and to some extent, reflecting the systemic health state of the human body, which can be utilized for diagnosis.[37] Many protective mechanisms are involved in defending oral cavity from invasion of pathogens and other hazardous species. Antimicrobial peptides (AMPs) are typical host-defence molecules that can contest against the invasive microbes originating from salivary glands and oral epithelium, and play a key role in the immune activation and wound healing processes.[14] Oral cavity also contains many biomarkers produced from stimulated inflammatory cells, including tumour necrosis factors, interleukins, and chemokines, which could provide valuable information for diagnosis, prevention, and treatment of chronic diseases.[38, 39] In addition, many antioxidants are present in the oral cavity, which form a defensive barrier against the oxidative stress caused by bacteria and inflammation. These biomarkers also reflect the health states of the human body, ranging from oral diseases (periodontitis, oral cancer, etc.) to systemic diseases (diabetes, rheumatoid arthritis, etc.).[40-42]

2.3 Oral cavity as an indicator for physical and mental conditions

The main connection of oral cavity with the circulatory system is the transportation of biomolecules from blood capillaries to oral fluid, through diffusion, active transport, and ultrafiltration mechanisms.[17] The Drug distribution in the oral fluid depends on their chemical properties, including solubility, molecular weight, and degree of protein binding etc.[43] To systematically assess the pharmacokinetic performance of different drugs, N. Idkaidek and T. Arafatof proposed a Salivary Excretion Classification System (SECS) based on drug high (H)/low (L) permeability and high (H)/low (L) fraction unbound to plasma proteins. this provides a standard for salivary drug pharmacokinetics monitoring.[44] Most of drugs are highly bounded to blood proteins, and only the free fraction is pharmacologically active.[45] The free fraction of drug could infiltrate through the salivary tissues (capillary wall, basement membrane, and membrane of the salivary gland epithelial cells) and eventually enter saliva.[46] Besides the drug concentration, data of actual salivary pH and flow rate are also critical in pharmacokinetics investigation.[47, 48]

Many disease-related biomarkers in blood can also afflux into the oral fluid, providing the potential for diagnosis. For example, there is a significant correlation between salivary and serum urea and creatinine, which can be utilized as non-invasively biomarkers for renal diseases, diabetic and hypertension.[49, 50] Moreover, oral fluid can also be utilized for monitoring the level of hormones in blood.[51] Above all, the non-invasive sampling process of oral fluids and its close correlation with blood made it a promising alternative for continuous drug monitoring and other pharmacokinetics applications.

Table 1. Comparison of skin electronics, intraoral biosensors and implantable devices in the aspect of biophysical information and biochemical information.

Types	Biophysical Information	Biochemical Information
Skin Electronics	❖ **Anatomical characters:** multilayer structures; Large detection area with relative plain structures;[9] ❖ **Biomarkers:** Electrical (ECG, EMG, EEG),[52-54] Mechanical (strain, blood pressure),[55, 56] temperature,[57] optical signal[58]; ❖ **Established techniques:** Highly integrated, multifunctional, multi-modal, conformable and stretchable electronic networks.[7]	❖ **Biochemical environment:** Environmental impact and contamination, pH, hydration states, unstable sweat rates;[10] ❖ **Biomarkers:** Environmental (hydration state, pH, pollutants),[59] Systemic (electrolytes, metabolites), and pharmacokinetic (Methylxanthine Drugs);[10] ❖ **Established techniques:** Sampling methods (microfluidics, iontophoresis) and sensing techniques (electrical, optical, etc.);[6, 60]
Intraoral Biosensors	❖ **Anatomical characters:** Well-arranged soft (Tongue, buccal, etc.) and hard (hard palate, teeth, etc.) tissues.[61] ❖ **Biomarkers:** Tongue movement,[62] head impact[63], and orthodontic force;[64] ❖ **Established techniques:** tongue–computer interface,[62] smart mouthguard[63], and orthodontics;[64]	❖ **Biochemical environment:** Environmental (Bacteria, food, air, etc.), oral and systematic species (electrolytes, enzymes, and other metabolisms);[64] ❖ **Biomarkers:** Environmental (infectious microbes),[65] intraoral (Periodontics),[66] systemic (VOCs, electrolytes and metabolites, macromolecules, enzymes, and microbes) and pharmacokinetic (Free section of plasma);[15, 31, 37, 39, 67] ❖ **Established techniques:** Primary trials (Mouthguard, tooth adhesive electrodes, oral brackets);[43, 45]
Implantable Devices	❖ **Anatomical characters:** Muscle movements and altered tissue stiffness.[61] ❖ **Biomarkers:** ECG,[68] EEG,[69] blood pressure;[70] ❖ **Established techniques:** Biocompatible materials[71] and minimally invasive techniques (syringe injectable electronics,[69] absorbable electrodes[72])	❖ **Biochemical environment:** Aggressive ions, ROS species, hostile immune response and foreign body rejection;[71] ❖ **Biomarkers:** Comprehensive and reliable biomarkers for disease and Pharmacokinetics (including protein bounded and unbounded);[73-75] ❖ **Established techniques:** Antifouling strategies;[74] Integrated monitor and therapy techniques (Glucose management);[75]

Moreover, oral cavity can also reflect the mental states of a person. The saliva flow rate and composition respond to the innervation of parasympathetic or sympathetic nerves. High-flow, low protein saliva was produced under the innervation of the parasympathetic nerve, while low-flow, high-protein saliva was produced under sympathetic impulses.[26] To objectively reflecting the mental state, the monitoring process should be carried out at relaxing state, which made the saliva-based diagnosis advantageous over clinical diagnosis.[76] The activity of salivary amylase can act as an indicator of the sympathetic nervous system activity. Many POC detecting methods were developed to detect its activity, which were utilized for self-reported psychological state monitoring in a variety of laboratory and naturalistic studies.[77]

3. Intraoral biosensors as promising supplements for skin electronics and implantable devices

The integration of medical science with modern science and technologies greatly facilitated the prosperity of health care monitoring devices, of which skin electronics and implantable devices were investigated. many health care monitoring techniques were established, regarding the anatomical characters and sensing environment of their targeting organs. These well-established techniques also prompt the emerging of devices that accommodated by other body sites. As the connecting point of the environment and human systems, oral cavity contains many characteristic biophysical and biochemical signals, which could become an attractive location for designing health care monitoring devices. We will discuss the characters of intraoral biosensors compared with skin electronics and implantable devices from the aspect of biophysical and biochemical information (Table 1). The possibilities of transferring techniques established in skin electronics and implantable devices to the intraoral biosensors are also discussed.

3.1 Biophysical information

The anatomical characters of target tissues need to be considered for the proper accommodation of medical devices. Human skin possesses integrated multilayer structures, with widely spread sensing networks, acting as a shield to protect our body from the invasion of the external environment.[9] The large detection area with relative plain structures endows the skin electronics with the place and comfort capability. The implantable devices can encounter more complex mechanical situations.[71] Different targeted tissues have specific stiffnesses, which would also change according to their pathological conditions.[78] Many tissues involved continuous muscle (ranging from cardiac, gastro-intestinal to skeletal muscles) movement, which will affect the performance of the devices.[79] As a result, highly conformable and adaptable materials are necessary to reduce injury and minimize adverse influences on targeted cells or organs.[80-82] Oral cavity has well-arranged soft (such as tongue and buccal) and hard (hard palate, teeth, etc) structures, at the same time, these structures have well-defined movement mode. Many oral structures can be utilized to attach intraoral devices, with little interference to the normal function.[61]

There are many valuable physical (electrical, mechanical, etc.) biomarkers in the human body reflecting the health status, which can be transmitted through the high impedance tissues from the inner organs. Skin electronics are advantageous at monitoring these physical biomarkers, including electrical signals (ECG, EMG, and EEG, etc.),[52-54] mechanical (heart rate, blood pressure, etc.)[55, 56] considering the non-invasive character. Besides, the detection capability of many environment-related signals (temperature,[57] and optical signals[58]) can also be incorporated into the skin electronics to augment the function of human skins. A highly integrated skin electronic networks have been built, which exhibit multifunctional, multi-modal conformable and stretchable electronics. Implantable devices are characterized for their detection accuracy, as well as the integrated diagnosis and therapy platform.[61, 83] The mechanical (blood pressure)[70] and electrical (ECG, EEG)[68, 69] signals can be obtained directly from the pathological sites, which could at the same time provide external stimulus or drugs to repair the functions of targeted organs.[84, 85] Oral cavity contains many characteristic biomarkers that are different from that absent from skins and inner organs. For instance, tongue movement has been utilized to construct tongue-computer interfaces, which help the spinal cord injured peoples to control the computer and wheelchair.[62] A commercialized smart mouthguard was designed to monitoring the head impact for intensive sports.[63] Moreover, incorporating force detectors inside the brackets could provide precise force profiling and accelerate the orthodontics processes.[64]

3.2 Biochemical information

The biochemical environment has a significant impact on the performance of medical devices. The sensing processes of skin electronics are dependent on the sweat rates and susceptive to many environmental factors, including temperature, contaminations, pH, hydration states etc.[10] Despite the segregation of environmental impacts, the implantable devices can encounter many hostile situations, including degradative enzymes, high concentration of ions, oxidation stress and so on.[86] Differently, oral cavity is the interface of the environment and human systems, undertaking the task for the matter exchanging processes. As a result, the intraoral biosensor can encounter stresses both from the environment (bacteria, food, air, etc.) and human systems (electrolytes, enzymes, and other metabolisms, etc.).[67]

The biochemical signals on skins are more likely to reflect the environmental circumstances, such as hydration state, pH, and pollutants.[59] While the diagnosis value of these signals for systemic diseases is mediocre, due to the filtration effect of the skin tissues as well as the influence of environment.[10] The implantable devices mainly target the blood or the interstitial fluid of the subcutaneous space, which can provide comprehensive and valid pathological or pharmacokinetic information for the patients and physicians to predict or diagnose diseases.[73-75] Different from the skins and inner organs, oral cavity contains abundant environmental (infectious microbes),[65] intraoral (periodontics),[66] systemic (VOCs, electrolytes and metabolites, macromolecules, enzymes and microbes)[15, 31, 37, 39, 67] and pharmacokinetic (free section of plasma) [43, 45] biomarkers, which could provide complementary information to skin electronics and implantable devices, establishing more comprehensive health care monitoring systems.

3.3 Transforming established techniques for intraoral biosensors

With the development of modern medicine, material science, electronics, computer science and communication technologies, health care monitoring devices (especially skin electronics and implantable devices) have attracted attention. Many techniques have been established to overcome arising challenges. For the skin electronics, highly integrated, multifunctional, multi-modal, conformable and stretchable electronic networks were fabricated to detect the biophysical signals[7]. At the same time, many sampling methods and sensing techniques were also established for biochemical signals detection. As for the implantable devices, many biocompatible materials[71], minimal invasive techniques[69, 72] antifouling strategies[74] as well as integrated monitor and therapy techniques[75] are developed. Despite a few primary trials for the oral related devices, the development of intraoral devices is still far from reaching its limit.[43, 45, 62-64] Techniques established in the skin electronics and implantable devices could provide abundant methods and inspirations for the design of new intraoral biosensors, which will be further illustrated in the following sections.

4. Design strategies for intraoral biosensors

4.1 Diagnostic databases in oral cavity

Oral fluids (also known as whole saliva) have drawn much interest due to its abundant physiological information and non-invasive nature. Researchers from chemistry, biological, medical, engineering technologies and other disciplines have made their efforts to develop separation and analysis techniques, which greatly enriched the diagnostic databases for the intraoral biosensors.[67, 87-89] For example, the microbiomes were investigated through PCR, bacteria microarrays, quantitative 16S rRNA gene sequencing, human-microbe identification microarrays and so on.[90] Proteomics, genomics, and metabolomics were screened through many integrated technologies, ranging from traditional biological techniques (gel electrophoresis, DNA hybridization, ELISA, protein immunoblot techniques, etc) to well-developed chemical detection methods (including, Nuclear magnetic resonance spectroscopy, mass spectrometry, high-performance liquid chromatography, capillary electrophoresis time of flight mass spectroscopy etc.)[91-93] According to the types of diseases, these biomarkers are cataloged for the diagnosis of oral diseases and systemic diseases.

Oral diseases include tooth decay, peri-implantitis, and oral cancer, which can be accurately diagnosed due to direct access.[37, 94] Periodontitis is a typical oral disease, which is characterized by chronic inflammation in subgingival areas, accompanied by tissue breakdown, vascular permeability and so on. The progression of periodontitis is also related to the

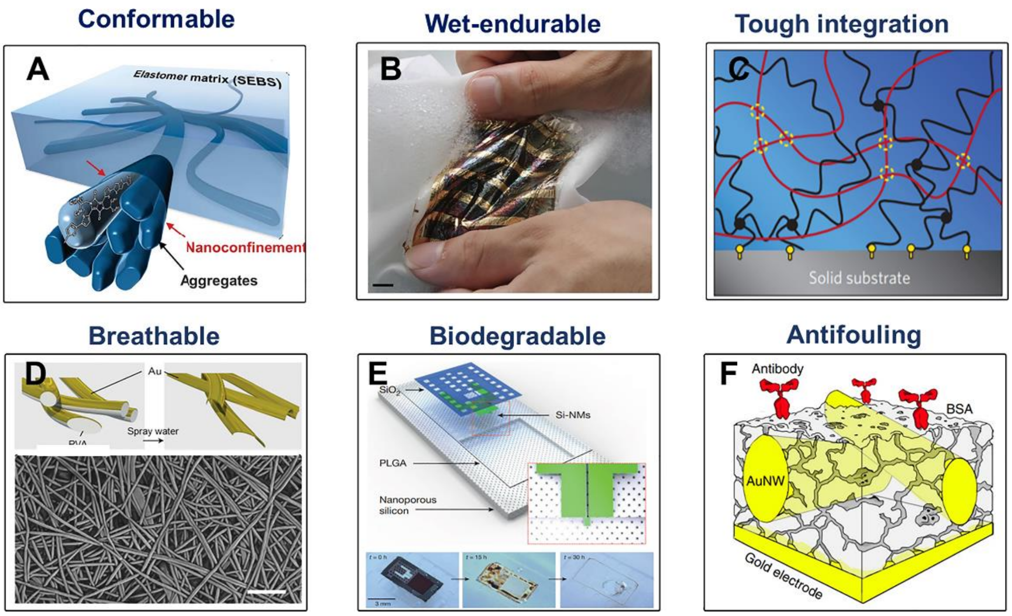

Figure 3. Material design for intraoral biosensors. (A) Schematic of 3D structure of the conformable thin film transistors (TFT) composed of elastic substrates (SEBS) and embedded nanoscale networks (DPPT-TT). (Reproduced with permission from ref. 105.). (C) Photograph of the wet-endurable devices conforming to a dress shirt. Scale bar, 1 cm. (Reproduced with permission from ref. 108.) (C) Design strategy for tough bonding of hydrogels to diverse solids. Long-chain polymer networks with covalent crosslinks to achieve covalently bonding on the solid surfaces and mechanically dissipative components with reversible crosslinks to further enhance interfacial toughness. (Reproduced with permission from ref. 109.) (D) Fabrication process and SEM image of Au nano-mesh conductors: PVA substrate was removed by spraying water. Scale bar, 5μm. (Reproduced with permission from ref. 110.) (E) Schematic illustration of biodegradable pressure sensor. The inset shows the location of the silicon nano-membrane (Si-NM) strain gauge. Bottom images shows the dissolution process (0 h, 15 h, 30 h) of the biodegradable sensor in an aqueous buffer solution (pH 12) at room temperature. (Reproduced with permission from ref. 112.) (F) Schematic of the porous antifouling coating on a gold electrode. The matrix contains glutaraldehyde (GA) cross-linked bovine serum albumin (BSA) supported by gold nano-wires. (Reproduced with permission from ref. 113.)

migration of the microbiome community biomass and community structure in the subgingival area, which can act as indicators for the developmental stages of periodontitis.[66] Moreover, the broken tissue can increase vascular permeability of the plasma into saliva, which eventually results in the steady metabolism flow of a series of inflammation associated metabolites.[95]

Oral fluids can also provide plenty of physiological information for systemic diseases. *P. gingivalis* is a keystone pathogen in periodontitis, which can secrete the *P. gingivalis*-derived peptidyl arginine deiminase (PPAD). Many systemic chronic inflammatory diseases, such as rheumatoid arthritis (RA), atherosclerosis (AS), and Alzheimer's disease (AD) are related to the *P. gingivalis* and PPAD.[96, 97] Recently, J. Potempa et al. have found direct proof for the *P. gingivalis* infection relation with AD in mice. They found that the infection of *P. gingivalis* in mice oral cavity can lead to increased production of aβ_{1-42} in brain. At the same time, the toxic proteases (named gingipains) can exert detrimental effects on the tau protein, leading to the further progression of AD. It is worth mentioning that, the neurotoxicity of gingipains was blocked after interacting with designed inhibitors, which prove a new strategy to treat *P. gingivalis* colonization and neurodegeneration.[98, 99]

4.2 Promising techniques for the intraoral biosensors

Material basis

The evolution of skin electronics and implantable devices have greatly promoted the design of new materials and advanced processing methods. The skin electronics mainly handle the issues of the environmental interface, adherence and comfort of the device to the skin. Accordingly, they have developed many techniques (such as photoetching, screen printing, and 3D printing) to process a series of materials that are suitable

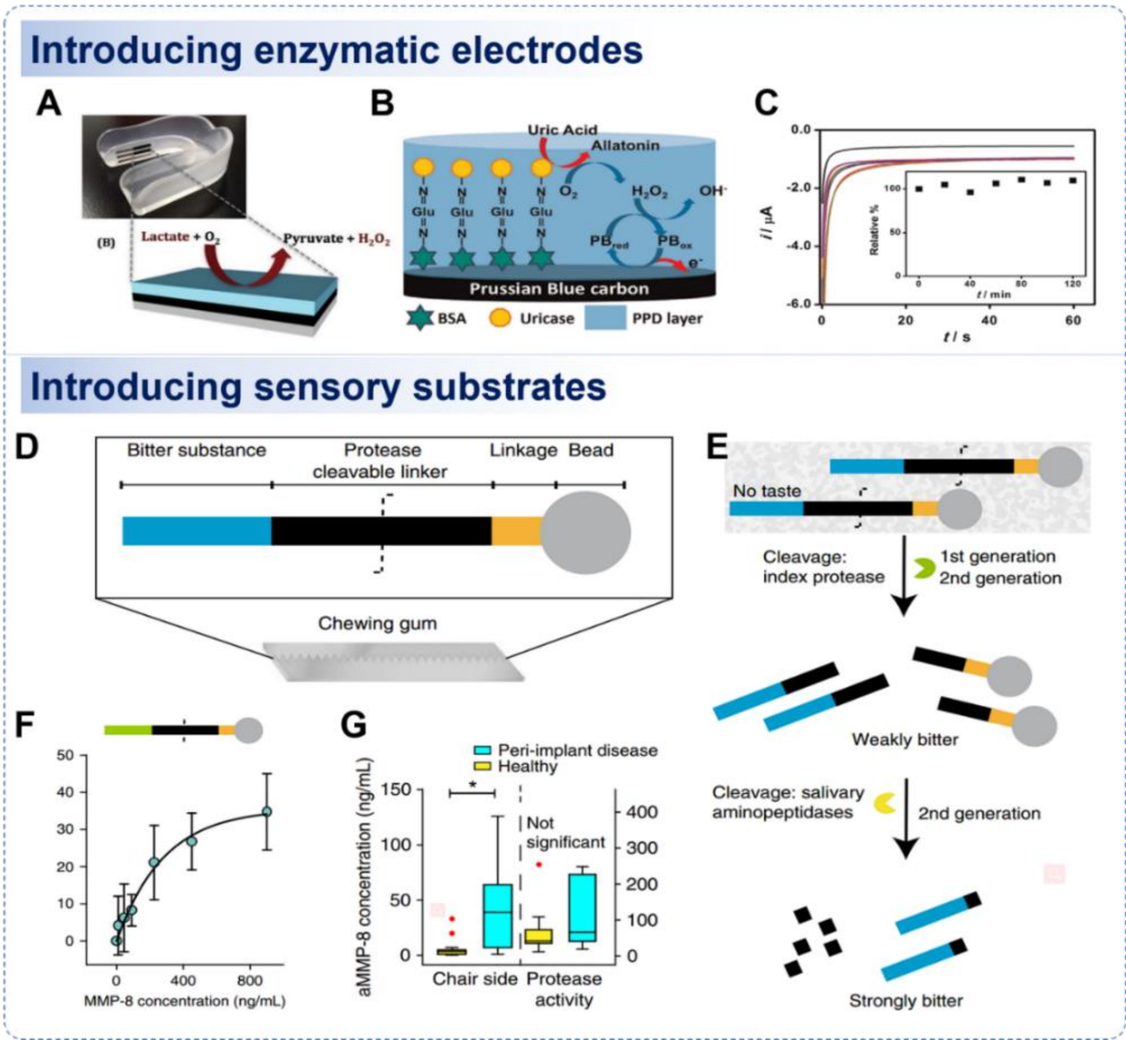

Figure 4. Sensing Methods for intraoral biosensors. (A-C) Introducing enzymatic electrodes for metabolites sensing. (A) Photograph of the mouthguard biosensor for lactate. (Reproduced with permission from ref. 117.) (B) The construction of uric acid sensor on Prussian-Blue carbon working electrode. (C) The electrochemical performance of the mouthguard biosensor in undiluted human saliva; (Reproduced with permission from ref. 13.) (D-G) Introducing protease cleavable sensory substrates for peri-implant disease diagnosis. (D) Illustration of the particle-bound protease cleavable linkers (PCL) denatonium conjugates. The bitter substances were covalently connected to the linkages bead through the PCL. (E) The two-step bitter taste generation process for the PCL substrates. The PCL substrates were cleaved by salivary MMPs to generate weakly bitter taste, and subsequently cleaved by salivary aminopeptidases to generate strong bitter. (F) Cleavage of peptide sensors consisting of PCL as a function of MMP-8 concentration incubated for 60 min. (G) sensing performance for the PCL sensor towards MMP-8 in sulcus fluid (chair side) and protease activity from saliva (QuickZyme MMP-8 activity test). Sulcus fluid and saliva were collected from with peri-implant diseases (n=19) and healthy control (n=14). (Reproduced with permission from ref. 119.)

for soft electronics [6, 100-102] These materials include the elastomeric substrates (such as Silk, PDMS, ecoflex, polyurethane), and conductive materials (carbon materials, conjugated polymers, metal nanowires, etc.).[7, 53, 103, 104] Many performances of these materials are also desired for intraoral biosensors. For example, the conformable materials are desirable for their good fitting and comfortable wearing in oral cavity (Figure 3A).[105] Considering the saliva secretion in oral cavity, wet materials (Such as hydrogels) or wet-endurable materials are preferred for their function in the wet environment of oral cavity (Figure 3B).[106-108] Additionally, tough integration of these wet materials with different solid substrates is also necessary for the stable performance of intraoral biosensors (Figure 3C).[109]

Material designs for implantable devices mainly focus on reducing invasiveness and resisting hostile immune response and foreign body rejection.[71] As many oral tissues (buccal mucosa, gingiva *et al.*) are similar to that of the inner organs, these design concepts and merits of materials can also be adapted to the intraoral sensors, such as breathable materials that can avoid inflammatory (Figure 3D),[110, 111] absorbable or biodegradable materials that can minimize the invasion (Figure 3E).[112] Moreover, similar to blood and interstitial fluid, saliva contains many macromolecules and metabolites, the antifouling ability of electrodes is also necessary for long-term monitoring (Figure 3F).[113] Regarding the biocompatibility of materials in biomedical applications, a series of regulations and risk-management systems were established to guarantee their safety to human body, these standards should be seriously followed when designing intraoral biosensors.[114]

Sensing methods

Despite the unique and abundant signals in the oral cavity compared to skin and inner organs, the sensing techniques developed for these biomarkers are not as abundant as the skin electronic and implantable devices. However, intraoral biosensors hold high potential, where the established sensing techniques in the skin electronics and implantable devices can be adjusted and applied in the intraoral biosensors.

The sampling processes of skin electronics mainly focus on the elimination of environmental contaminations, and a series of promising techniques have been established owing to the matured manufacture procedures [115, 116] Moreover, many targeting electrodes were designed to detect biochemical biomarkers, ranging from pH, ion (Na^+, K^+, Cl^- etc.), to macromolecules (proteins, nucleic acids, etc.) and metabolisms (glucose, lactic acid etc.).[4] These targeting methods greatly enriched the toolbox for designing intraoral biosensors. Inspired by their sweat sensing techniques, Wang group first proposed an amperometric mouthguard biosensor to detect salivary lactate, which can be integrated into a mouthguard (Figure 4A). As a proof of concept, they demonstrated the selective and stable detection of lactate in whole human saliva in vitro for over a 2 h operation. [117] Then, they integrated the wireless electronics to get a wearable salivary uric acid mouthguard biosensor. Poly(o-phenylenediamine) (PPD) was utilized to embed the uricase and Prussian-Blue (PB) acts as the electron carrier for the amperometric detection of uric acid (Figure 4B). The sensor stability was evaluated by analyzing undiluted human saliva. As shown in Figure 4C, the mouthguard sensor exhibited a stable response to the salivary uric acid for over 2 h with little biofouling issues.[13]

Implantable devices mainly handle invasive issues and the hostile chemical environment in the inner organs. An intuitive strategy is to minimize the size of the electrodes, Hunt et al. designed a suite of integrated glass microelectrodes, which can be utilized for the simultaneous acquisition of multimodal brain electrophysiology in vivo.[118] To minimize the invasiveness during the installation of implant devices, J. Liu et al. proposed a micro-springe injectable strategy to deliver flexible electronics to internal regions of targets.[69] The springe injection enabled the interpenetrating flexible electronics with 3D structures through a rigid shell, providing a reliable platform for delivering and installation of flexible electronics. Biofouling of the implanted electrodes is one of the main concerned due to the hostile chemical environment.[74] To solve this issue in the continuous glucose monitoring, X. Xie et al. designed an anti-fouling zwitterionic polymer, which can greatly reduce the noise signal after coating to the sensors, realizing continuous glucose monitoring in mice and non-human primates without the need for recalibration. It is worth mentioning that, the coated sensors significantly reduced immune responses. The sensing environment encountered in the intraoral biosensors may be different from that of implantable devices, but they share some common challenges such as mechanical and chemical instability of the sensor, as well as biofouling problems. For these cases, we can get inspirations from established techniques, which could provide a wealth of instructive strategies for intraoral biosensors.

Besides learning from the established techniques from skin electronics and implantable devices, the unique characteristics of oral cavity can also be utilized to design intraoral biosensors. Taking advantage of the taste buds in oral cavity, J. Ritzer et al. proposed the sensory chewing gums for oral inflammation diagnosis.[119] Instead of introducing a detector, the sensory substrates containing protease cleavable linker between bitter substances and beads were introduced into oral cavity as the indicator for the inflammation indicator (Figure 4D). The peptide sensor was designed to undergo a two-step generation process: firstly cleaved by the targeted MMP-8 to generate a weak bitter, with subsequent cleavage by aminopeptidases to boost bitterness (Figure 4E). The catalysis ability of MMP-8 towards the PCL was first investigated in vitro (Figure 4F). Subsequently, the capability of the PCL for discrimination of peri-implant disease and healthy subjects was demonstrated (Figure 4G). This chewing gum sensor can inspire more designs for detecting enzymes by introducing relative substrates.

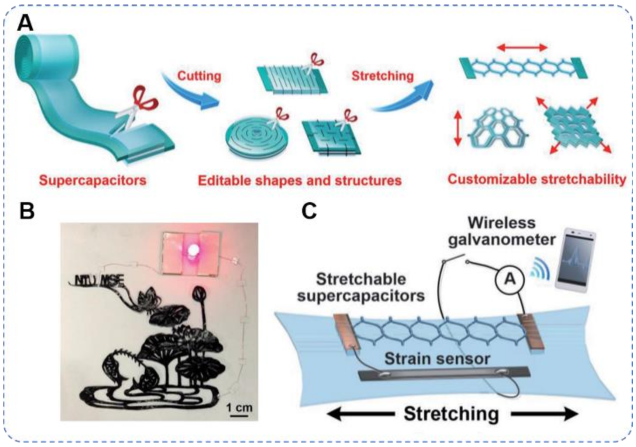

Figure 5 Editable and stretchable energy supercapacitors for energy supply for biosensors. (A) Illustration of the edit process for supercapacitors with different shapes and structures. (B) Complicated and delicate paper-cutting supply power for the LED light. (C) The stretching process of the integrated sensors and supercapacitors. (Reproduced with permission from ref. 124.)

Wearable energy source and signal transmitting

Wearable energy storage devices are preferred for the development of wearable sensors.[120-122] One strategy is to develop wearable biofuel cells, which were designed to harnessing energy from bio-fluids (such as sweat, tears and saliva) through the enzymatic reactions. The biofuel cells can either generate sensing signals or supply energy for connected wearable sensors.[123] Another strategy is to design conformable supercapacitors. Chen group reported a stretchable supercapacitor through paper cut methods, which endowed the supercapacitors with high conformability (Figure 5A).[124] The supercapacitors have good adaptability and stretchability, which can be edited into many desirable shapes, at the same time retaining high energy supply (Figure 5B). As a demonstration, the supercapacitors were edited into a honeycomb-like structure, which was then connected with a strain sensor to provide the energy, exhibiting stable performance for the linear signals of the outputs (Figure 5C).

Despite the conformability and customizability of wearable energy sources, it is ideal to transmit the sensing signals without the existing of energy inside the oral cavity to eliminate the safety issues. Many wireless communication technologies have been adapted for biosensors to collect physiological data *in situ*, process and transmit these data to remote devices. The radio-frequency identification (RFID) and near-field communication (NFC) are the most used techniques for intraoral biosensors.[125] M. C. McAlpine group reported a graphene-based bacteria sensor, which was incorporated into a resonant coil to eliminate the need for on-board power (Figure 6A).[126] To demonstrate the conformability, they transferred the bacteria sensor to a tooth in vitro, which could lead to the impedance

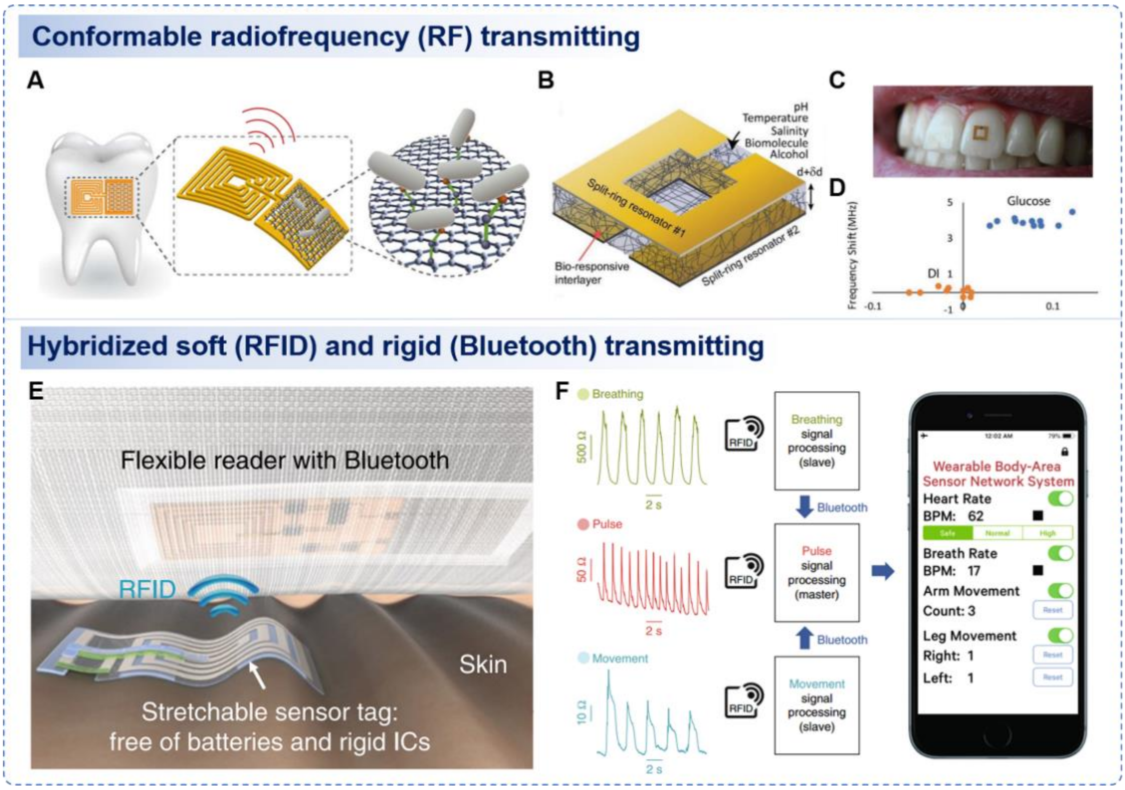

Figure 6. Signal transmitting techniques for intraoral biosensors. (A-C) Conformable radiofrequency (RF) transmitting methods (A) illustration of the sensing mechanism of graphene wireless nano-sensor for the wireless detection of bacteria. The wireless signal was obtained upon the binding of pathogenic bacteria by peptides self-assembled on the graphene. (Reproduced with permission from ref. 126.) (B) Schematic illustration of the broadside coupled split-ring resonators with responsive hydrogel as the interlayer. Resonant frequency and amplitude of the changed after exposed to targets (changing thickness and dielectric constant). (C) Demonstration of the trilayer sensor adhered on a human subject's tooth for intraoral sensing. (D) Response of the trilayer sensor during multiple repeated solution changes between DI water and glucose solution (0.5 g L^{-1}). (Reproduced with permission from ref. 127.) (E, F) Wireless signal transmitting via hybridization of stretchable sensors and high-performance silicon electronics. (E) Schematic illustration of the interconnection between rigid and soft components. (F) Signal transmitting procedures of the resistive strain sensors, from the signal acquisition (breathing, pulse and arm movement), data sending via RFID, data collecting and processing, and eventually transmitting to the smartphone via Bluetooth. (Reproduced with permission from ref. 128.)

change of the graphene sensor. P. Tseng et al. designed a trilayer conformal radiofrequency (RF) sensor, which was composed of an active layer encapsulated inside two reverse-facing resonators (Figure 6B).[127] The conformable RF sensors can be adhered to the teeth of a human subject and realize in situ PBS and glucose monitoring (Figure 6C, D). More recently, Bao and Chen group reported a bodyNET system, which could combine the stretchable and conformable RFID circuits with the rigid Bluetooth transmitting modules (Figure 6E, F).[128] This provides a new solution to solve mechanical incompatibility issues between soft electronics and high-performance silicon electronics.

Conformable electronics

For the intraoral biosensors, flexibility and conformability are preferred to connect various sections. Many strategies have been proposed during the evolution processes of skin electronics and implantable devices, including the material designs (or molecule design) to structure designs.[129] From the aspect of materials, incorporating conductive inks or nanomaterials with elastomers are prevalent strategies.[100] D. H. Kim group reported a highly conductive and stretchable Ag–Au composites for wearable and implantable bioelectronics, which was fabricated through the drying of the complex of ultralong Au-coated Ag nanowires, SBS elastomer and hexamine solution (Figure 7A, B).[68] The high conductivity and stretchability were resulted from the formation of microstructures of Ag–Au nanowire-rich region and an SBS-rich region (Figure 7C, D). The elastomer can also act as the substrate to support the conformable conductors, Chen reported the conformable microelectrode arrays with wavy structures through the pre-stretching of PDMS substrate, which exhibited excellent performance for the in vivo Electrophysiological monitoring.[130] Structure design can become a promising alternative to transform traditional rigid conductors into conformable electrodes.[131] Someya group fabricated the electrodes on an ultrathin (1 mm) polymer foils, enabling the electronic circuit to be ultra-flexible and achieve imperceptible performance (Figure 7E).[132] The obtained device has ultralight (3g m^{-2}) properties, which made the device much lighter than a feather (Figure 7F). The attachment of the device on the upper jaw indicates that this device has good conformability for intraoral sensing applications (Figure 7G).

Systematic Integration

To fulfill the actual application of biosensors, each step should be systematically assessed and designed to organically integrate different sections, including substrates, electrodes, power supplements, signal obtain, process and transmitting techniques, etc.[133, 134] Y. Lee et al. reported a well-integrated intraoral sodium sensor, which could quantify sodium intake *in situ* for hypertension management.[135] They elaborately designed the devices by transfer printing and hard–soft integration techniques to adapt it to the unique character of oral cavity (Figure 8A, B). From the engineering aspect, they laminated the electronics onto an oral retainer, which could be fixed to the upper jaw without interfering with food intake processes. The multilayer electronics include flexible interconnection electrodes that can accommodate dynamic mechanical stress. At the same time, supportive materials have breathable, biocompatible virtue for comfort wearing (Figure 8C, D). The sensing electrodes were also designed with microstructures, with ion-selective sodium electrode as the working electrode, Ag/AgCl as the reference electrode (Figure

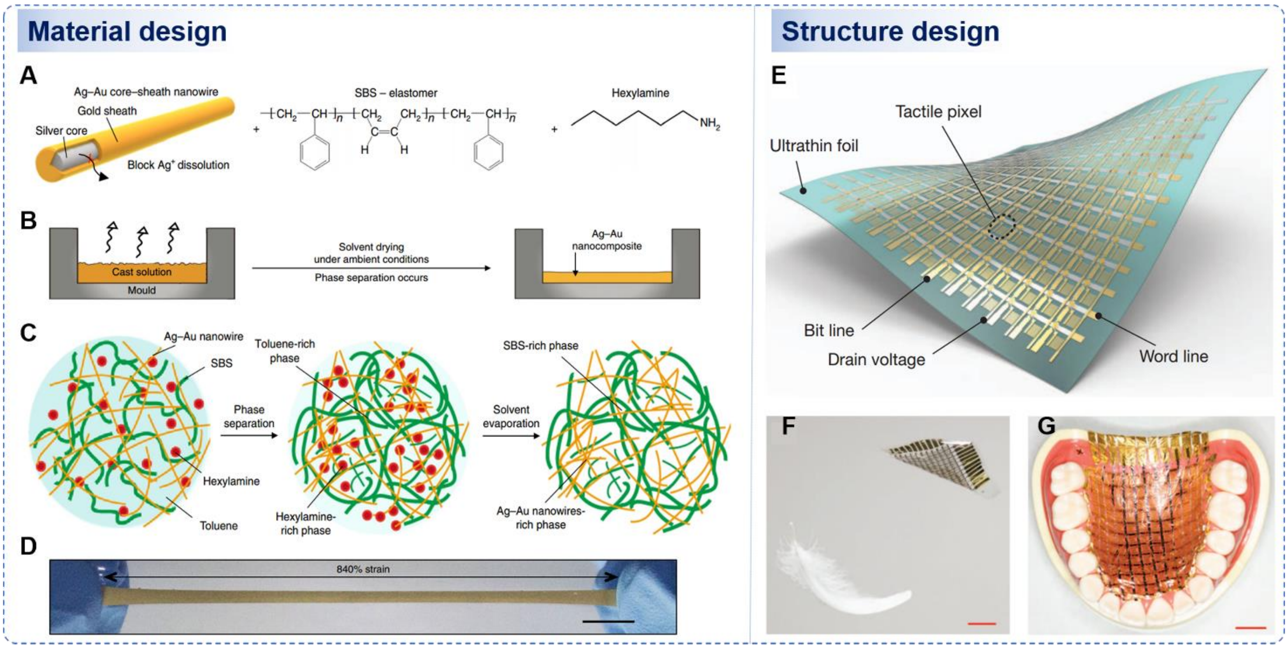

Figure 7. Conformable electronics for the development of intraoral biosensors. (A-D) Material design of the stretchable and conformable bioelectronics. (Reproduced with permission from ref. 68) (A) The Ag-Au nanocomposite were composed of Ag–Au nanowires, SBS elastomer and hexylamine ligands. (B) Solvent-drying methods for processing Ag-Au nanocomposites. (C) Schematic illustration of the microstructures of Ag–Au nanowire nanocomposite during the phase separation and solvent evaporation process. (D) The demonstration of the stretchability of the obtained Ag–Au nanocomposite. Scale bars, 10 mm. (E-G) ultra-lightweight and imperceptible performances. (E) Illustration of the conformable electronics for resistive tactile sensors. (F) Demonstration of the lightweight electronics by comparing the floating rate with a feather. Scale bar, 1 cm. (G) Tactile sensor sheet tightly conforming to a model of the human upper jaw. Scale bar, 1 cm. (Reproduced with permission from ref. 132.)

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8E, F). The overall sodium sensing process is illustrated in the flowchart, the potential variation due to different sodium concentrations was loaded on the op-amp circuit and then converted into a digital signal, which was wirelessly transmitted to a portable device (Figure 8G). The real-time quantification of sodium intake was demonstrated on a human subject, which could become a promising tool for hypertension management (Figure 8H, I).

5. Conclusions and perspectives

Oral cavity as an important interface between the environment and human systems should have drawn more attention as a target site for health care monitoring. Among which, saliva as the main liquid sample in oral cavity has been widely investigated, various modern separation and analysis techniques have been utilized to screen the biomarkers in a high throughput manner, which provides the fundamental database for the development of oral cavity-based diagnosis. At the same time, a series of portable devices (along with different saliva sampling methods) meant for the POC diagnosis also provide more prototypes for intraoral biosensors. From the aspect of materials and electronics, we have witnessed the prosperity of the skin electronics and implantable devices, which greatly promote the evolution of related disciplines, including the material science, soft electronics, computer and communication techniques et al. Taking advantage of the unique characters of oral cavity, these established techniques could become a wealth toolbox for designing intraoral biosensors.

Despite the promising future ahead, many challenges remain to be settled to apply the intraoral biosensors to daily health care monitoring. Here, we listed a few actions that can be taken to accelerate the development of intraoral biosensors (Figure 9).

Establish standardized and valid diagnostic databases

Most of the biomarkers obtained are based on saliva collected by different sampling methods, which would greatly affect the consistency of the data obtained from different sources. A sampling standard should be established to accelerate the data sharing of the oral-based database.[136] Moreover, saliva flow rate and composition vary significantly with the extent of simulation (food, physical exercise, medicine, mental stress, etc.).[137] As a result, the location of intraoral biosensors should be considered, and inner standards should be set to calculate these fluctuations.[138] Furthermore, race, age, gender, circadian and circannual could greatly affect the concentration of biomarkers, so multifactorial data processing methods for these variations are necessary.

Enrich material and engineering toolboxes

Despite that soft and conformable materials have contributed to the prosperity of wearable health monitoring devices, many issues remained for the intraoral sensors: (1) Fouling problems induced by salvia and the diet; (2) mechanical disturbances during the food intake process and breathing. Fortunately, many potential material and engineering techniques can be adapted to settle these issues. Firstly, new functional elements can be introduced solely or as additives into the existed soft material toolboxes, including the physical (mechanical, thermal, photo, magnetic, etc.), chemical (pH, ion, Ox-Red, etc.) and

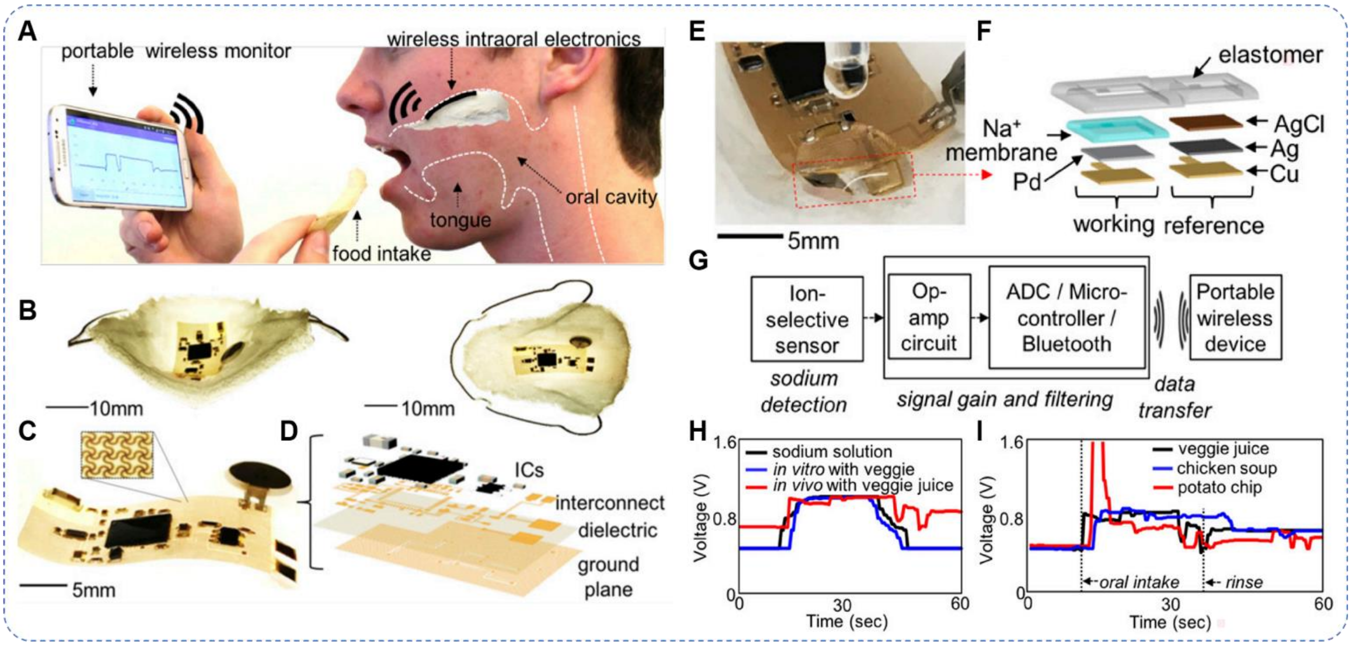

Figure 8. Integrated intraoral biosensors for real-time quantification of sodium intake toward hypertension management. (A) Overview of the intraoral biosensor for real-time sodium intake quantification during food intake process, the obtained signal was wirelessly transmitted to the smartphone. (B) Photos of the electronics configured in a conformable mouth retainer. (C) Zoomed-in photo of wireless biosensor. (D) Illustration of the multilayer composition of electronics in C. (E) Photo of the sodium sensing electrodes. (F) Multilayer structures for the sodium sensor, composed of working and reference electrodes. (G) Flowchart for the intraoral sodium sensor from detection, signal processing, to data transfer. (H) In vivo and real-time detection of veggie juice with high sodium concentration. (I) In vivo, real-time measurement of different types of foods. (Reproduced with permission from ref. 135.)

biological responsive elements (glucose, enzymes, inflammation, etc.).[139-143] Additionally, new material modification concepts can be adopted to tune the functions of materials existed in the toolboxes, such as the superamolecular systems, bioorthogonal reactions, and other conjugation methods.[144, 145] More material engineering methods can be developed via the inspiration of biological tissues, agents, and behaviors.[146] A representative example is mimicking the uniform structures of natural wood by the directional freeze drying methods.[147]

Transform from traditional oral products

Oral medicine is an important medical branch. During the development of oral science, a series of oral biomaterials and techniques have been developed for clinical applications, which provide abundant resources for designing intraoral biosensors.[148] Oral mucosal films have been widely utilized for tailor-made and controlled drug delivery as an alternative administrative route.[149] The mucosal film can be designed to attach to a defined application site of the oral mucosa that has been commercialized for the treatment of intraoral diseases (such as sublingual or buccal side). By incorporating conformable electronics into these well-investigated mucoadhesive materials, many intraoral biosensors can be fabricated. Mouth guards firstly designed for protection in professional boxing, have been widely used in sports protection, orthodontists, and other health care products.[150] Owing to the convenient worn and replacement characters, mouthguards can become good carriers to incorporate intraoral sensors for sport-related health monitoring. Besides the soft and conformal devices, oral cavity can also accommodate many other hard and rigid oral products, which have been widely utilized for traditional medicine but have not been considered for the intraoral sensors, such as smart brackets for orthodontics [151]and dentures[152].

Incorporate multiple sensing techniques

Electrical sensing techniques (potentiometric, impedance, capacitive, etc.) have been prevalent for the wearable and implantable devices due to their rapid and sensitive detection. These techniques can be developed into a sensing platform by incorporating more sensing techniques, which exert the advantages and compensate for the limitation of single techniques. For example, many fluorescent probes (such as traditional organic probes,[153] conjugated polymers,[154] AIE molecules[155], etc.) have good biocompatibility, extensive targeting capability, high sensitivity, and selectivity. These advantages can be incorporated to the electrical sensing platform by designing wearable fluorescence exciting devices (such as OLED) and photodetectors.[156, 157] In another case, Chen group reported a cascade tactile chemomechanical device, which can transform the bio-recognition process to the mechanical signal (gas pressure), followed by the transformation of mechanical to electrical signal by a tactile sensor.[158] This strategy can be utilized to develop multi-step signal transduction systems.

Construct systematic data collecting and processing platform

The prosperity of wearable and implantable devices greatly expands the medical database. As a result, a systematic data collection and processing platform are necessary to exert their potentials in modern medicine. Data collecting is a crucial step that decides the reliability of subsequent data processing and outcome. As a result, coherent and comprehensive guidelines need to developed to pivotally evaluate the accuracy of the biomarker for clinical application.[159] After further screening and integration, these medical data from different sources can be compiled into a comprehensive database, which can be learned by artificial intelligence (AI) to provide more reliable outputs for disease diagnosis and therapy.[160-162]

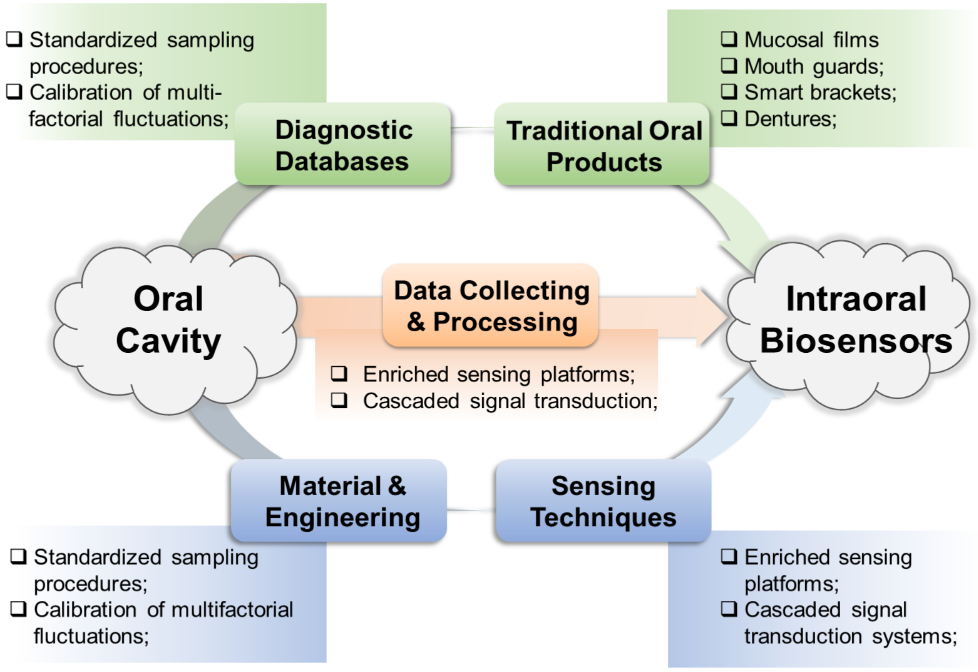

Figure 9. Multi-disciplinary approaches for developing intraoral biosensors.

In conclusion, oral cavity contains a wealth of biomarkers that can be utilized for non-invasive health care monitoring. Together with the development of saliva-based clinical and portable diagnosis techniques, many prototypes for intraoral biosensors emerged and exhibited a promising development trend. It is easy to envision that, intraoral biosensors together with skin electronics, implantable devices and other forms of medical devices can form an integral health care monitoring network, which would provide comprehensive and valid physical and mental information to eliminate diagnostic errors, prevent upcoming diseases and improve the quality as well as the efficiency of therapy.

Conflicts of interest

There are no conflicts to declare.

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