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Glucose Sensing in Saliva

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Glucose plays critical roles in many human body functions, above all as a source of energy. Abnormal levels of glucose are correlated to different diseases, importantly including diabetes. As such, quantification of glucose levels in body fluids is essential for health monitoring. Blood tests and, more recently, portable interstitial fluid tests, currently represent the benchmarks for glucose detection. Inconvenient invasive methods such as blood tests pose burdens on both patients and the healthcare system. In this review, noninvasive approaches to measure glucose levels in the human body are discussed, utilizing saliva as an alternative to conventional blood samples. Techniques explored and with the potential to enhance accuracy and their associated challenges are discussed.

1. Introduction

Glucose serves as the primary energy source for cellular functions in the human body. Thus, its level in blood and its regulation are of paramount importance. The nervous and endocrine systems play major roles in regulating glucose, principally by the opposing and balanced actions of glucagon (increasing blood sugar level) and insulin (decreasing blood sugar level), referred to as glucose homeostasis.[1] This process is pivotal for balancing healthy blood sugar levels in the body, which is in the narrow range of 4–6 mM. However, metabolic disorders involving glucose processing are quite common and they can lead to various glucose-related diseases, above all diabetes.

Diabetes mellitus is a chronic condition characterized by elevated concentrations of glucose in the bloodstream, stemming from either insufficient insulin secretion or impaired cellular response to insulin. The International Diabetes Federation estimates that over half a billion people worldwide are affected by diabetes mellitus, i.e., ≈10.5% of the adult population (20–79 years old), with nearly half of them unaware of their condition.[2] Moreover, this number is projected to grow to more than 1.3 billion people by 2050. Early diagnostics and continuous glycemic monitoring are crucial to providing real-time data to patients and preventing diabetes-associated chronic complications, such as heart disease and kidney failure.[3]

Current at-home testing methods of glucose detection include finger-prick blood glucose testing and the utilization of wearable patches for continuous glucose monitoring, which have been fundamental in managing diabetes and other diseases. However, they still present certain limitations, such as possible discomfort and pain for patients together with the risk of infection.[4]

As a result, there has been a significant research endeavor in the field of glucose point-of-care testing (POCT) in recent decades, with particular attention to noninvasively accessible body fluids, i.e., urine, tears, and saliva. These innovations aim to revolutionize glucose monitoring, making it painless, patient-friendly, and accessible, with great potential for commercialization. Among these body fluids, saliva has been at the center of a number of studies, due to its high accessibility, the noninvasive and relatively simple collection methods, and the fairly supported correlation between blood and salivary glucose levels—albeit still debated.[5]

While the management and screening of diabetes is likely the most common application for glucose monitoring, both in blood and saliva, it is not the only one. In fact, abnormal levels of salivary glucose have also been correlated with dental issues, such as periodontitis, retinopathy, neuropathy, glomerular filtration, peripheral arterial diseases, and myocardial infarction.[6] All these conditions have been correlated to diabetes. Outside of disease

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management, monitoring of glucose levels has shown potential for nutrition and diet, with glucose being correlated to nutritional habits and body-mass index, stress management, and physical activity and sports performance.[7] However, each these applications has different limitations and conditions (e.g., sample volume, response rate required, body fluid of interest).

Previous reviews have primarily focused on traditional methods for glucose monitoring or other noninvasive fluids, mainly sweat and interstitial fluids. Here, we provide a comprehensive overview of the advancements in glucose sensing in saliva. Saliva offers several advantages, such as easy collection that would reduce discomfort and the risk of infection (as compared to blood tests). Moreover, technological advances have improved the sensitivity and selectivity of saliva-based approaches, making them promising alternatives. While other reviews have analyzed the pros and cons of utilizing saliva for novel noninvasive solutions for POCT,[8] we note the lack of detailed analyses of the developed sensors and designs, particularly regarding their performance in terms of sensitivity, selectivity, and tests with saliva samples.

Here, we provide a brief introduction to glucose metabolism, discussing its concentration and role in various body fluids, before delving into the sensing strategies employed or potentially applicable in saliva. The sensors described are categorized based on their detection mechanisms, with common features and limitations emphasized. Lastly, we look ahead to future directions, opportunities, and challenges in this field.

2. Glucose Metabolism

Glucose is a monosaccharide with a chemical formula $C_6H_{12}O_6$ that occurs naturally in honey, fruits, and vegetables.[9] Therefore, it can be introduced into the body directly, where it is absorbed in the buccal cavity and transported into the bloodstream.[10] Alternatively, glucose can be produced in the body via the digestion of carbohydrates, such as other monosaccharides (e.g., fructose and galactose), disaccharides (e.g., sucrose and maltose), α-glucan oligosaccharides, and some polysaccharides, e.g., starch. In fact, the digestion of carbohydrates leads to the formation of monosaccharides, 80% of which is glucose.[11] The digestion of starch starts in the mouth, due to the enzyme amylase contained in saliva, and ends in the duodenum (small intestine), where pancreatic amylase completes the digestion of starch and the brush border enzymes present on the microvilli, i.e., maltase, lactase, and sucrase, hydrolyze maltose, lactose, and sucrose, respectively, into monosaccharides.[11,12] As these enzymes can only break down α1-4 and α1-6 bonds found in starch and disaccharides, respectively, other plant polysaccharides presenting β-linked units, such as pectin and cellulose, cannot be digested, and hence transfer to the large intestine where they are digested via fermentation processes, producing short-chain fatty acids.[9,11] These polysaccharides are also known as non-starch, non-digestible, and non-α-glucan polysaccharides.

As described above, the consumption of carbohydrates is essential to produce glucose, which is one of the main molecules used to produce energy in the body. Glucose undergoes an enzymatic process called glycolysis, which includes a series of cascade reactions that transform glucose into two pyruvate molecules.[12,13] This process is accompanied by the formation of highly energetic molecules, such as adenosine-5′-triphosphate (ATP), which is consumed by cells to power other internal processes. Each glucose molecule produces eight ATP through glycolysis.[12] This process occurs in the cytoplasm of cells and can occur in both the presence and absence of oxygen, albeit yielding different amounts of ATP.

Diet and digestion of carbohydrates are not the only ways that humans intake glucose. Glucose can be produced from glycogen through a process similar to glycolysis called glycogenolysis. Glycogen is synthesized via glycogenesis in the liver and in the skeletal muscles when glucose is in excess and cannot be used immediately. As such, glycogen serves as glucose storage in the body, and through glycogenolysis, it can be a source of energy during times of need.[12] In a similar fashion, other non-carbohydrate molecules, e.g., pyruvate, lactate, glycerol, and the carbon backbone of glucogenic amino acids, can be converted into glucose, when necessary. This process is called gluconeogenesis, occurs mostly in the liver, kidneys, and brain, and is critical during periods of starvation and fasting. Gluconeogenesis can be viewed as the inverse of glycolysis, incorporating reversible reactions that occur in the opposite direction. This process generates glucose, which is then transported through the bloodstream to the tissues in need, particularly the brain.[12,13]

These processes are regulated via hormones, which promote or inhibit some metabolic pathways. The two main hormones involved in glucose regulation are insulin and glucagon. While both are secreted by the pancreas, in the Islet of Langerhans, they have opposite effects.[14] Insulin is released when glucose blood concentration is elevated and promotes the uptake of glucose into the muscles, e.g., heart and skeletal muscles, and the formation of glycogen. Hence, insulin promotes the transport of glucose away from the blood and upregulates glycolysis.[12–14] On the other hand, glucagon is secreted when the glucose blood level is low. As such, glucagon promotes both glycogenolysis and gluconeogenesis to increase the number of glucose molecules available.[12–14] Other hormones involved in the regulation of blood glucose are somatostatin, cortisol, epinephrine, thyroxine, the growth hormone, and the adrenocorticotropic hormone.[14]

Excess glucose, aside from undergoing conversion back into glycogen, may also be expelled through urine when the concentration of plasma glucose exceeds 11 mM, which is the renal function limit beyond which the kidney cannot reabsorb additional glucose.[12] Glucose can also be expelled through sweat, likely diffusing from the blood and interstitial fluid (ISF).[13] **Figure 1** shows a high-level sketch of glucose metabolism and the body fluids where it can be found.

3. Body Fluids Containing Glucose

At present, blood glucose monitoring based on electrochemical methods persists as the most practical and adopted choice for POCT and have undergone substantial evolution since its introduction to the market in the 1990s, including improved accuracy, reduced sample volume, analysis time, and cost-effectiveness.[5j] However, the reliance of these analyses on fingertip blood collection leads to patient discomfort and heightens the risk of infection when employed frequently as in the case of diabetic patients.[4]

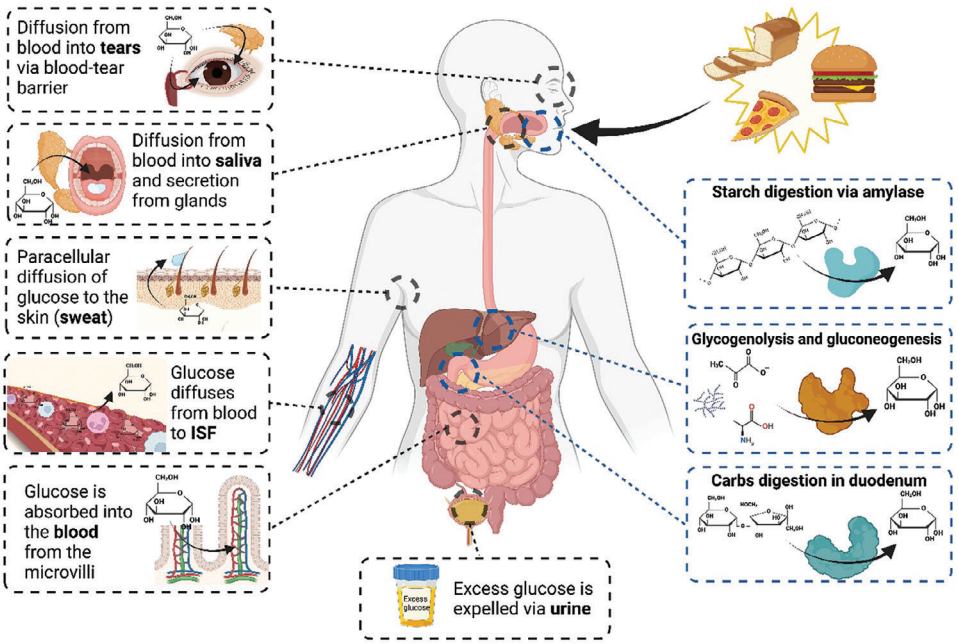

Figure 1. (Right) Glucose metabolism processes and (left) how glucose ends up in different bodily fluids.

Apart from blood, glucose is also present in other bodily fluids including sweat, urine, ISF, tears, and saliva. These fluids have been considered as possible alternative media to monitor blood glucose levels by noninvasive or minimally invasive methods. These fluids differ not only by the source and mechanism by which glucose flows into them but also by their concentration ranges. The exact ranges of glucose levels in different body fluids for both healthy and diabetic patients are not uniform in the literature, as shown in **Table 1**. These discrepancies in concentration ranges are possibly due to differences in the populations studied and the nature of the studies; some differences are quite significant.

The ISF represents one of the most targeted body fluids to monitor blood glucose levels.[5j] The peculiar characteristics of blood capillaries (e.g., area-to-volume ratio, flow rate, pressure), allow efficient fluid and analyte exchange between blood and ISF,[29] leading to strong correlations between the glucose levels in the two fluids.[15] Different methods have been explored to extract ISF from the subcutaneous tissue to the skin surface, such as minimally invasive needle-based and microdialysis probe devices.[30] However, their limited life span, stability, and the necessity to puncture the skin represent obstacles to their consumer acceptance.[1b,5j] To avoid the use of needles, reverse iontophoresis has also been studied to extract ISF from the skin efficiently,

Table 1. Glucose source and concentration in healthy and diabetic people in each body fluid. The concentration values found between the health and diabetic columns indicate the range for both healthy and diabetic patients.

Body fluid	Glucose passage mechanism from blood	Concentration range in healthy people [μM]	Concentration range in diabetic patients [μM]
Blood	–	4,100–6,900[15]	
		4900–6900[16]	2000–40 000[16,17]
		4000–8000[18]	2000–30 000[18]
ISF	Diffusion through capillary walls	3900–6600[19]	1990–22 200[20]
Urine	Excess glucose filtered by the kidneys is expelled through urine	2780–5550[21]	> 5,550[21]
Sweat	Paracellular diffusion into epithelium cells	10–200[22]	/
		20–600[5j]	
		10–1000[23]	
Tears	Diffusion through acinar and ductal cell layer	50–500[24]	500–5,000[24]
		0–3,600[25]	3,600–4,700[25]
Saliva	Paracellular diffusion through gingival sulcus	238–716[26]	555–1176[26]
		2–200[27]	167–207[28]
		44–58[3a]	17–1008[5i]

but the possible interferences with sweat and the reported irritations on human skin hindered the commercialization of the devices based on this technology.[18]

The correlations between biomarkers, such as creatinine, albumin, and other proteins in urine and blood have significant importance in medical diagnostics.[31] These biomarkers, indicative of health conditions including kidney dysfunctions, diabetes, and other metabolic disorders, are commonly monitored in clinical settings. In particular, glycosuria, namely the presence of sugars in urine, is a strong symptom of diabetes or the diminished ability of kidneys to filter glucose, meaning that the glucose concentration in urine could be used as an indicator for the blood level.[32] Plasma glucose is indeed filtered in the kidneys and then reabsorbed until it reaches a concentration in the blood of ≈11 mM.[33] Hence, detection of glucose in urine is only suitable for diabetic patients exhibiting moderately high levels (i.e., above 11 mM) of blood glucose. Moreover, urine's unreliable correlation with blood glucose levels, due to its time lag and variable renal threshold (54–300 mg dl^{-1}) in diabetics, makes it an unreliable medium for continuous glucose monitoring. Additionally, the use of the current popular medication for type-2 diabetes such as sodium–glucose cotransporter-2 inhibitors, and SGLT2 inhibitors, which lower blood sugar by excreting it in urine, further reduces the accuracy of measuring glucose levels using urine as a body fluid.[34]

Sweat is one of the most promising biofluids for continuous and noninvasive monitoring of various analytes, due to the potential design and implementation of affordable wearable devices, ranging from clothing and bracelets to watches, patches, and tattoos.[35] Notably, glucose rapidly diffuses from ISF to the skin surface by paracellular diffusion through the epithelium cell layer.[36] Despite this connection, results regarding the correlation of glucose levels between sweat and blood remain contradictory. Moreover, variations in operational parameters, skin contamination, and irreproducible sample extraction rates, with stimulation and iontophoresis required to provide reliable samples, limit the development of reliable sweat-based glucose sensors.[5j,37]

Many analytes present in blood, including glucose, have also been found in the fluids surrounding the eye and the ocular tissue.[38] The two fluids are separated by the "blood-tear barrier," a layer of acinar and ductal cells within the lacrimal gland, the conjunctive epithelium, and the corneal epithelium, which allows efficient diffusion of blood components.[38] Thus, tears have been considered as a readily available and noninvasive detection fluid, and different devices, such as contact lenses,[39] and eyeglasses,[40] have been developed. However, tear analyses face challenges such as difficult extraction, uncontrollable secretion rates compared to other body fluids,[15] and issues related to powering the glucose sensor on contact lenses for autonomous operation and wireless data transmission.[41]

Saliva is principally produced by three main glands, the parotid, submandibular, and sublingual, and other minor glands, which contribute less in terms of volume (≈10% of the total) but more in terms of blood plasma components. Glucose, in particular, is able to diffuse easily from blood plasma through the membranes of the blood vessels to the gingival fluid through the gingival sulcus.[21] Despite some conflicting data, most recent studies indicate strong correlations between glucose levels in saliva and blood plasma (**Table 2**).[42] These variations are likely due to the range of factors that affect glucose concentration in saliva. **Table 3** provides an overview of the reported salivary glucose ranges in both healthy individuals and diabetic patients across various studies.[3a,5b–f,i,43] Differences in sampling methods such as time after the most recent meal, stimulating salivation, and mouth rinsing, and in sample treatment (e.g., centrifugation and filtration) contribute to the wide range of reported concentrations. In fact, studies have shown that salivary glucose levels are strongly dependent on the collection time after the most recent meal, with glucose concentrations increasing more than two-fold after meals in some cases.[44] Other activities involving the mouth, such as drinking, chewing, smoking, and taking supplements also affect salivary glucose levels.[44a,45] These variations are to be expected, as salivary glucose diffuses from blood vessels, with blood glucose levels also being strongly affected by the timing of sampling (i.e., fasting, post-prandial, non-fasting).[46] Due to this relationship, the daily fluctuations of glucose levels in blood and saliva are similar, with delays that appear to be less than 15 min between blood and saliva levels, according to the limited literature available.[44b,47] Other factors that can impact measured glucose levels in saliva include the method of saliva sampling (stimulated vs unstimulated, parotid, sublingual, whole), mouth hygiene habits (brushing, rinsing), and patient characteristics (body mass index—BMI, diabetes).[44] As a consequence, while intra-study comparisons show significant differences between healthy and diseased ranges, the significance diminishes when comparing finding across studies. An additional point of consideration pertains to the definition of healthy and diabetic patients, which lacks uniformity. Circumstances may arise where individuals with pre-diabetes conditions are included in the healthy subject groups. Furthermore, Gupta et al. highlight a distinction in salivary glucose levels between patients with controlled and uncontrolled diabetes.[5f] Given the relative lack of regulation in this field, drawing definitive conclusions remains challenging. Nevertheless, the potential for salivary glucose screening and monitoring remains promising, particularly as standardized practices continue to evolve. Despite salivary glucose's lower accuracy and specificity compared to blood glucose in diagnosing diabetes, the analysis of glucose in saliva can serve as an excellent tool for pre-screening, monitoring, and rapid and more frequent assessment. This utility is further facilitated by the simplicity and non-invasiveness of saliva collection.[5e]

4. Glucose Salivary Sensors

Saliva has been gaining traction as a possible biofluid alternative to blood for common biomarkers analyses. Saliva contains many biomarkers for health monitoring, including lactate, uric acid and cholesterol.[8b] However, care must be taken for using saliva for development of a POCT devices due to its complex chemical composition and the typically lower concentration of biomarkers of interest compared to blood. While saliva is mainly composed of water, it also contains electrolytes (Na^+, K^+, Cl^-, Ca^+, etc.), mucus, enzymes (e.g., amylases, lipases, proteases), antibodies, proteins, peptides, DNA, RNA, metabolites (e.g., dopamine, fatty acids, serotonin), and inflammatory biomarkers such as cytokines and chemokines.[51] Such a rich environment can cause interferences during the detection process, either by passivating

Table 2. List of studies assessing the correlation between blood and salivary glucose in healthy and diabetic populations.

Cohort sample (total)	Correlation in healthy subjects	*p*-value	Correlation in diabetic subjects	*p*-value	Method of detection of glucose	Year	Notes	Ref.
80		Yes ($R^2 = 0.9153$)			GOx/peroxidase	2022	Unstimulated parotid salivary glucose level is better correlated to blood glucose	[5a]
40	Yes	< 0.01	Yes	< 0.01	GOx/peroxidase	2019	Salivary glucose level was inconsistent with the severity of diabetes	[5b]
75		Yes ($p < 0.001$)			GOx/peroxidase	2018	Participants were divided into three groups based on their fasting glucose level in the blood	[43c]
2332	Yes	< 0.001	Yes	< 0.001	N/A	2018	Review/meta-analysis	[48]
200	Yes	< 0.01	Yes	< 0.05	GOx/peroxidase	2019	N/A	[5c]
100	Yes	<0.0001	Yes	<0.001[a)]	N/A	2023	The diabetes group was subdivided into normal, pre-obese, and obese based on BMI	[5d]
138		Yes ($p < 0.0001$)			AccuCheck glucometer (for capillary blood) and ELITech Glucose reagent—Gox/peroxidase (for serum and saliva)	2019	Saliva glucose proved less specific and accurate in diagnosing diabetes compared to blood	[5e]
90		Yes ($p < 0.01$)			GOx/peroxidase method	2020	Postprandial correlation goes down to $p < 0.05$	[5f]
110		Yes ($p < 0.0001$)			GOx/TBHBA	2021	Parotid saliva was proven to be the best sampling method	[49]
120	Yes	= 0.001	Yes	< 0.001	GOx end-point assay	2017	Population was divided into three groups: control, controlled diabetes, and uncontrolled diabetes.	[5g]
100	N/A		Yes	< 0.001	GOx/peroxidase method in photocolorimeter	2017	N/A	[50]

[a)] Value is for pre-obese.

electrodes and/or by acting as electroactive interferents.[52] As a result, saliva samples are often processed or membranes are employed to achieve cleaner signals.[8a] Considering all these issues, detecting glucose in saliva is not prohibitive, as its lowest concentration is on the order of micromolar.

Table 4 lists some of the electrochemical sensors recently designed and applied for salivary glucose detection. They are mostly amperometric and can be divided into enzymatic and non-enzymatic, as summarized in **Figure 2**. As noted in Figure 2, other bioelectronic sensors[31,53] could be of use for measuring glucose in saliva and are worth exploring for this application.

4.1. Enzymatic Sensors

Enzymatic glucose sensors have been widely studied for all biofluids containing glucose. These sensors adopt enzymes capable of oxidizing glucose, providing highly selective designs that mitigate the influence of possible interfering species. Among these enzymes, glucose oxidase (GOx) emerges as the preferred option for this purpose, due to its high selectivity and effective performance across various pH and temperature conditions.[5j] Over the years, GOx has been employed for three distinct enzymatic sensor generations, which differ in the electron transfer mechanism between the enzyme co-factor, typically flavin adenine dinucleotide (FAD), and the electrode.

In the first generation of enzymatic biosensors, glucose is oxidized in the presence of oxygen by the action of GOx generating hydrogen peroxide which reacts with the electrode to indicate the amount of consumed glucose. The occurring reaction chain is reported in Equations (1–3).

$$\text{Glucose} + \text{GOx} - \text{FAD} \rightarrow \text{Gluconic acid} + \text{GOx} - \text{FADH}_2 \quad (1)$$

$$\text{GOx} - \text{FADH}_2 + \text{O}_2 \rightarrow \text{GOx} - \text{FAD} + \text{H}_2\text{O}_2 \quad (2)$$

$$\text{H}_2\text{O}_2 \rightarrow \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \quad (3)$$

These sensors are usually simple and economical but the reliance of the reaction chain on the presence of dissolved oxygen in the sensing solution can lead to significant analytical errors due to the limited O_2 solubility in biological fluids (the so-called "oxygen deficit").[5j] Moreover, high potentials are required for detecting H_2O_2, leading to the likelihood of interferences from co-existing electroactive species such as acetaminophen (AP), ascorbic acid (AA), or uric acid (UA).[5j] Different materials have been adopted in first-generation saliva glucose biosensors to address

Table 3. Salivary glucose concentration ranges were reported.

Sampling method	Rinse	Sample pretreatment	Time after meal [min]	Number and type of patients	Glucose concentration [μM][b)]	Ref.
Unstimulated whole saliva without swallowing for 5 min	Yes	Centrifugation	N/A	100—healthy	238–716	[26]
				100—diabetic	555–1176	
Unstimulated whole saliva, cotton rolls onto sublingual caruncular for 5 min	Yes	Ultrafiltration	Fasting[a)]	6—healthy	2–200	[43a]
Stimulated whole saliva	Yes	Filtration	N/A	2—healthy	44–58	[3a]
Unstimulated saliva, cotton	Yes	Centrifugation	Fasting[a)]	38—healthy	73.6–85.2	[43b]
				84—diabetic	167.3–207.3	
Stimulated saliva, cotton				38—healthy	28.0–36.8	
				84—diabetic	167.9–207.1	
Unstimulated saliva	Yes	Centrifugation	Fasting[a)]	15—healthy	28–129	[5i]
				106—diabetic	17–1008	
Unstimulated whole saliva	Yes	None	90	20—healthy	5.2–45.3	[5b]
				20—diabetic	51–354	
Unstimulated whole saliva	Yes	Centrifugation	Fasting[a)]	25—healthy	155–434	[43c]
				25—diabetic	339–827	
Unstimulated whole saliva	No	None	120	100—healthy	122–248	[5c]
				100—diabetic	162–389	
Unstimulated whole saliva	N/A	N/A	N/A	50—healthy	112–399	[5d]
				50—diabetic	381–1168	
Unstimulated whole saliva	Yes	Centrifugation	Fasting[a)]	59—healthy	170–470	[5e]
				79—diabetic	490–1350	
Unstimulated whole saliva	N/A	Centrifugation	Fasting[a)]	40—healthy	38.3–48.3	[5f]
				40—c. diabetic[c)]	194–346	
				40—u. diabetic[c)]	476–781	
			120	40—healthy	5866–8178	
				40—c. diabetic[c)]	9364–11267	
				40—u. diabetic[c)]	16678–23908	
			Random	40—healthy	5488–6876	
				40—c. diabetic[c)]	7717–9731	
				40—u. diabetic[c)]	14977–23033	
Unstimulated whole saliva	Yes	None	Fasting[a)]	40—healthy	434–616	[43d]
				60—diabetic	528–904	
Average	N/A	N/A	Fasting	Healthy	116–252	N/A
				Diabetic	291–686	
			Non-fasting	Healthy	1960–2686	
				Diabetic	6257–8933	

[a)] Any period above 6 h was considered fasting; [b)] When the range was not provided, the mean ± the standard deviation was used as the range; [c)] "c." stands for controlled and "u." stands for uncontrolled.

this issue. Prussian Blue (PB) has been extensively adopted as an electrocatalyst for selective and low-potential cathodic detection of H_2O_2.[54] García-Carmona et al. used a carbon-PB ink to print GOx-based electrodes on a PET substrate, resulting in improved detection range and selectivity.[55] Alternatively, noble metals (e.g., Pt, Pd, Rh) are able to reduce the operating potential and have recently been coupled to carrier materials, such as carbon nanomaterials and polymers, to improve the enzyme stability and to enhance the electron-transfer rate.[5j,53b] However, oxygen deficiency nonetheless hinders the performance of these sensors.

Second-generation sensors introduce co-substrates to replace oxygen in Equation (2), acting as synthetic electron mediators between the enzyme active site and the substrate. Ferrocene, ferricyanide, and their derivates are commonly adopted as mediators, together with other complex molecules such as tetrathiafulvalene and naphthoquinone.[56] These mediators offer fast electrode kinetics and good reversibility, reducing the risk of interferences.

In contrast, third-generation biosensors rely on direct electron transfer (DET) from the enzyme cofactor to the electrode substrate. This approach is contemplated in a few studies due to the deep position of the GOx redox centers.[5j,57] To this end

Table 4. Salivary glucose sensors. All the listed sensors are amperometric sensors. Abbreviations used are listed below the table in order of appearance.

Generation (if enzymatic)	Acronym	Substrate	Sensing materials	Membrane	Linear range [μM]	LOD [μM]	Sensitivity [μA $mM^{-1}cm^{-2}$]	Testing method	Selectivity	Ref.
Enzymatic – 1st generation	PETG/GOx/PMEHB	PETG	SPE with GOx mixed with PMEHB	Cellulose acetate	1.75–10^4	/	/	Immersed	UA, AA	[53b]
	PET/PB/GOx	PET	SPE with PB, GOx and chitosan	/	100–1.4*10^3	40	690	Flowing	UA, AA	[55]
Enzymatic – 2nd generation	PI/GOx/3D-CNAs	PI	SPE with GOx, NQ, and 3D carbon nanosphere network aerogel	Chitosan	5–4.5*10^6	0.48	/	Drop casting (0.3 μL)	/	[56]
	Paper/PEDOT:PSS/GOx/Fc	Paper	Inkjet-printed PEDOT:PSS, GOx, chitosan and ferrocene	Nafion	28–850	/	/	Drop casting (30 μL)	UA, AA, lactate	[90]
	ITO/TiO_2/PHT/GOx	Glass	TiO_2 nanoparticles and PHT onto indium-tin-oxide glass with GOx	/	55–1.7*10^4	34	/	/	Lysozyme, sucrose, LA	[85]
	Pt-MWCNTs/TTF/GOx	Polymer resin	Pt decorated multiwalled CNTs and TTF with GOx	Thermoplastic PU and PEG on paper, Nafion	100–1.4*10^3	/	5.3	Drop casting	Lactate, AA, UA, CA, NaCl, KCl, $CaCl_2$, NH_4Cl, albumin	[77]
Enzymatic – third generation	FTO-CNTs/PEI/GOx	Glass	CNTs on a fluorine-doped tin oxide-coated glass substrate and GOx	/	70–700	/	63.4	Immersed	AA, UA, dopamine	[57]
	Glass/Acid-CNTs/PPy/FTO/GOx	Glass	PPy on fluorine-doped tin oxide modified with acid-treated CNTs and GOx	/	10–700	/	95.3	Immersed	AA, UA, dopamine	[58]
Non-enzymatic	Cu_2O-NCs/graphene	Graphene	Cu_2O nanocubes on graphene strip	Nafion	2–1.7*10^4	0.23	36.4	Immersed	UA, AA, citric acid, dopamine	[65]
	Bronze	Bronze	Tin–copper alloy	/	20–320	/	770	Drop casting (30 μL)	UA, AA, dopamine, urea	[64]
	FTO/Au-CuO NR	Glass	Cu nanorods on fluorine-doped tin oxide and Au NP	/	5–1.3*10^3	0.17	2009	Immersed (30 mL)	UA, AA, dopamine, urea, sucrose	[68b]
	AAM/NNMBA/Au-SPE	Acrylamide	Electropolymerized acrylamide/Bis-Acrylamide on Au-SPE	/	10–330	3.3	/	Immersed	Lactose, sucrose	[69a]
	CuO-SnOx	Glassy carbon	SnOx-decorated CuO nanorods	Nafion	1–6*10^3	3.08	2303	Immersed	Dopamine, LA, AA, NaCl	[59]
	FTO/NiO	Glass	Porous nanostructured NiO on fluorine tin oxide	Nafion	5–825	0.084	2632	Immersed	AA, UA, dopamine, urea	[68a]
	$Ni(OH)_2$/AuNP/SPE	Graphite	$Ni(OH)_2$ + Au-NPs on SPE	/	100–2*10^3	400	/	Immersed	AA, dopamine	[60]

(*Continued*)

Table 4. (Continued)

Generation (if enzymatic)	Acronym	Substrate	Sensing materials	Membrane	Linear range [μM]	LOD [μM]	Sensitivity [μA $mM^{-1}cm^{-2}$]	Testing method	Selectivity	Ref.
	Ecoflex®/graphite/Au-NPs/GQDs	Polymer and Graphene	Au-NPs and graphene quantum dots	/	100–1.5*10^3	9.12	/	Immersed	tartrazine, sodium benzoate, nitrite, sodium bisulfite, fructose, AA	[68c]
	3D-CuO NFs	Copper	In situ grown 3D CuO nanoflake array	/	2–6*10^3	0.1	4954	Immersed	AA, dopamine, maltose, sucrose, galactose, mannose, lactose, fructose, amylase	[84b]
	C/NiCl(OH) NS/CC	Carbon cloth	NiCl(OH) nanosheet array	/	1–3.5*10^3	0.29	8052	Immersed	UA, AA, dopamine, fructose	[84a]
	Si/Ti/Au/Co_3O_4	Si wafer	Co_3O_4 needles anchored on an Au honeycomb-like framework	/	2–10^4	20	23.5	Immersed	UA, AA, dopamine, cortisol	[86]
	Cu-NPG/SPE	/	Cu-nanoporous Au structure on SPE	/	1–1.3*10^3	0.13	659.9	Immersed	AA, UA, NaCl, KCl, galactose, fructose, sucrose	[87]
	3D-MgO/CC	Carbon cloth	3D-MgO	/	40–6.9*10^3	0.41	198	Immersed	Maltose, mannose, AA, NaCl, lactose, UA, urea, thiourea, threonine, sucrose	[62]
	Au-CNT aerogel	CNT aerogel	Au-NPs sputtered carbon nanotube aerogel film	/	100–6*10^3	1.47	779	Immersed	Lactose, fructose, UA	[63]
	Cu-PT NPs/GCE	Glassy carbon	Cu-Pt NPs on a glassy carbon electrode (GCE)	/	10–750	1.8	2209	Immersed	Galactose, fructose, xylose, mannose, sucrose, acetaminophen, AA, UA, NaCl, KCl	[61]

PETG, poly(ethylene terephthalate glycol); PMEHB, poly(MPC-co-EHMA-co-MBP); UA, uric acid; AA, ascorbic acid; PET, poly(ethylene terephthalate); PB, Prussian blue; SPE, screen-printed electrode; NQ, 1,4-naphtoquinone; PI, polyimide; CNA, carbon nanosphere network aerogel; PEDOT:PSS, poly(3,4-ethylenedioxythiophene) poly(styrene sulfonate); Fc, ferrocene; ITO, indium tin oxide; PHT, poly(3-hexylthiophene); MWCNT, multi-wall carbon nanotubes; PU, polyurethane; PEG, poly(ethylene glycol); TTF, tetrathiafulvalene; FTO, fluorine tin oxide; CNT, carbon nanotube; PEI, polyethyleneimine; PPy, polypyrrole; NC, nanocube; NR, nanorods; AAM, acrylamide; NNMBA, N, N′-methylene bis-acrylamide; LA, lactic acid; NP, nanoparticle; GQD, graphene quantum dot; NF, nanoflake; NS, nanosheet; CC, carbon cloth; NPG, nonporous gold; GCE, glassy carbon electrode.

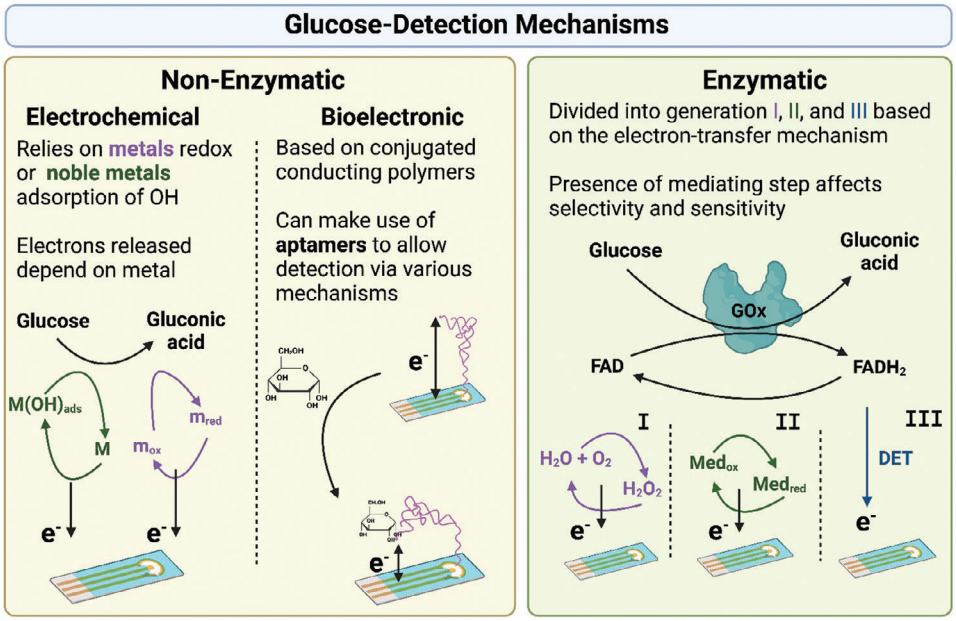

Figure 2. Glucose detection mechanisms of enzymatic and non-enzymatic sensors.

conductive nanomaterials, such as carbon nanotubes and metal nanoparticles, with high surface-to-volume ratios and electrical conductivity have been used to enhance sensitivity. As an example, fluorine-doped tin oxide conductive glass substrates modified with carbon nanotubes and GOx immobilized in different polymers[57,58] was applied for glucose detection in third-generation sensors for glucose detection within the range of 10–1000 μM.

4.2. Metal-Based Sensors

To replace GOx, most non-enzymatic sensors take advantage of the ability of metals to change electron valence and often employ nanostructures to increase sensitivity. Metals such as Cu,[59] Ni,[60] Pt,[61] Mg,[62] and Au,[63] can all be utilized as catalysts for the oxidation of glucose to gluconolactone (or gluconic acid). However, they could suffer from disadvantages such as poor selectivity,[5j] and requiring alkaline environments to catalyze the reaction, which would normally not be suitable for detection in the mildly acidic environment created by saliva.[64] Temporary alkaline conditions can be created by applying certain voltages to the sensing elements or, alternatively, the metal catalysts can be electro-oxidized to allow detection.[62]

The general process that leads to glucose detection, involves the reduction of the metal to either a hydroxy or oxyhydroxide state (e.g., Au–OH, CuOOH, NiOOH), which is then oxidized back to an oxide state. For example, for copper, the reaction can be summarized as:

$$Cu_2O + 2OH^- + H_2O \rightarrow 2Cu(OH)_2 + 2e^- \quad (4)$$

$$Cu(OH)_2 \rightarrow CuO + H_2O \quad (5)$$

$$CuO + OH^- \rightarrow CuOOH + e^- \quad (6)$$

$$CuOOH + \text{glucose} \rightarrow Cu(OH)_2 + \text{gluconic acid} \quad (7)$$

where the detection mechanism can either start from Cu_2O, $Cu(OH)_2$, or CuO depending on the initial state of the metal.[65] The overall reaction releases electrons to re-oxidize copper to Cu(III), so as to catalyze the further degradation of more glucose molecules. Other metals, such as Ni, Co, Zn, and Ti, undergo similar reactions.[66] These reactions only work in the case of chemical bonding between oxygen and the metal, and as such are not valid in the case of noble metals such as Au and Pt, where chemical bonding is replaced by adsorption, as per the following equations (Equation 8 and 9):

$$Au + OH^- \rightarrow Au(OH)_{ads} + e^- \quad (8)$$

$$Au(OH)_{ads} + \text{glucose} \rightarrow Au + \text{gluconic acid} + H_2O \quad (9)$$

Nanostructures are extensively used to improve sensitivity and to lower the limit of detection (LOD), by enhancing electron transfer and increasing the available surface area for reaction.[67] The shape of the nanostructure employed can vary greatly, as nanoparticles, nanorods, quantum dots, and nanosheets are all utilized.[59,60,62,63,65,68]

4.3. Other Non-Enzymatic Sensor Types

Other strategies for the non-enzymatic detection of glucose not involving metals have been investigated, such as molecularly imprinted polymers (MIPs),[69] or aptamers.[53a,70] MIPs have gained particular attention thanks to their robustness, high selectivity, and versatility in various applications such as sensing and drug delivery.[69a] MIP synthesis is typically achieved through polymerization in the presence of a template molecule and a

cross-linking agent, creating high-affinity binding sites, highly selective in shape, size, and chemical functionality. For glucose sensing, functional polymers like acrylamide are polymerized in the presence of glucose and crosslinking materials (e.g. *N,N′*-methylene bis-acrylamide).[69a] Electrochemical detection is then usually achieved by measuring the current change in response to glucose exposure. When glucose binds to MIP recognition cavities, it impedes electron transfer to the sensor's redox probe, allowing detection of glucose to levels as low as 3.32 μM in the case of Diouf et al..[69a] On the other hand, aptamer-based sensors rely on the formation of a conjugate with the analyte. For electrochemical transduction (e.g., the work described by Nguyen et al.) conjugation with glucose causes a change in current.[70] For aptamer-field effect transistors, the transduction is modified, and sensitivity covers six orders of magnitude in concentration.[53a]

Non-enzymatic glucose sensors have garnered attention due to their potential advantages. These sensors directly detect glucose in blood and other biological fluids without relying on enzymes. However, their limited prevalence can be attributed to two factors, a) monopoly of the enzymatic sensors by manufacturer to dominate the market, limiting the adoption of non-enzymatic sensors; b) manufacturing challenges for the cumbersome production of non-enzymatic glucose sensors, which reduces their scalability and hence may impact their applicability.[71] An attractive alternative is bioelectronic sensors, in which π-conjugated electrical conductors are paired biological entities, as in the case of the highly selective and specific aptamer-based field effect transistors (FETs) developed by Andrews, Weiss, Stojanović, and co-workers.[53a,72] The use of aptamers enables strong selectivity against interferents that could be closely related molecules. The sensors cover a wide range of concentrations (up to six orders of magnitude). They have recently been integrated into arrays in chips.[73] Further exploration of their application in saliva is warranted to determine their applicability in this complex medium as they have not been tested in saliva yet.

4.4. Sensor and Device Design

Humans produce on average between 0.5 and 1.5 L of saliva each day, most of which is secreted while eating.[74] Therefore, the saliva production rate is ≈0.3–0.4 mL min^{-1}. Thus, both saliva sampling and minimizing the required sample volume for analysis are essential factors in the successful development of point-of-care (POC) devices. Despite these issues, many studies in the literature require the sensor to be immersed in solutions of up to 30 mL (Table 4), making POCT applications untenable. The high volume needed for analysis in these cases is typically due to the use of standard three-electrode systems for amperometric detection design that electrochemical sensors have in common, regardless of whether enzymes are employed or not.

Sensor and device design are fundamental to minimizing the volumes of samples required, and some studies have been carried out to integrate sensing materials into everyday items. For instance, Chen et al. have inserted a three-electrode system into an electric toothbrush, lowering the amount of sample required to 30 μL.[64] Similarly, Liu et al. placed a three-electrode system including a carbon graphite ink working electrode, which was decorated with GOx at the back of a manual toothbrush.[75] They used this system for detection of glucose in a 400 μL sample that was not human saliva. García-Carmona et al. included a first-generation enzymatic glucose sensor in a pacifier.[55] Including the sensor in an item that is naturally kept in the mouth for extended periods of time can bypass the sample volume issue, even though some adult patients may not be inclined to use such devices. Arakawa et al., similarly to previous studies,[76] designed a mouthguard that included an enzymatic glucose sensor.[53b] While the level of comfort for users should be considered, this is another example of a device design that can bypass sample volume requirements, as the sensor is constantly exposed to the analyte.

Further, some studies involve using microfluidic settings to reduce the amount of sample required for analysis.[77] Microfluidic devices can drastically reduce the amount of reagents and analyte used, while also increasing throughput and time efficiency.[78] Vinoth et al. developed a multiplexed microfluidic device for the detection of metabolites in saliva and demonstrated successful and selective detection of glucose in human saliva.[77] Examples are shown in **Figure 3**. Some of these devices have been tested in real-life scenarios by continuously monitoring the glucose level in saliva for short periods of time. For example, the pacifier designed by García-Carmona et al. was tested for 30 min on healthy and diabetic patients, before and after a meal, demonstrating the ability to alert the wearer or the parents rapidly about abnormal glucose levels. Despite the technology's potential transferability to alternative designs and/or analytes, several challenges remain, mainly concerning stability and biofouling.[55] For other biomarker measurements (and proposed for glucose monitoring in saliva),[76,79] Wang and co-workers have developed an instrumented retainer with wireless communication for continuous monitoring.[75] Others have proposed denture- and dental tattoo-based sensors for continuous monitoring.[80] Implementing the technologies discussed in such devices would provide many advantages in the standardized collection and the personalized time series of data available.

4.5. Commercially Available Sensors and Patents

Many patents have been filed that relate to glucose sensing, particularly for continuous monitoring devices. Between 2000 and 2022, more than 6000 such patents were filed, with over 70% focusing on invasive and minimally invasive methods for monitoring glucose in blood or interstitial fluid (ISF).[68] Despite their widespread use, as highlighted in this Review, these technologies have a number of limitations, including patient discomfort, the need for calibration, and the risk of biofouling.

The development of innovative noninvasive POCT solutions has grown, increasing four-fold from 2000 to 2022.[81] Some designs collect samples from saliva or exhaled breath to measure glucose levels in these bodily fluids. However, these technologies are in their early stages and have not yet received Food and Drug Administration (FDA) approval for commercial use.

Companies such as Dongwoon Anatech and iQ Global Group have developed glucose-detection devices based on saliva. The D-SaLife device (Figure 3F),[82] created by Dongwoon Anatech, consists of a digital meter and a paper-based electrode decorated with gold and glucose oxidase (GOx). In this design, patients use a sy-

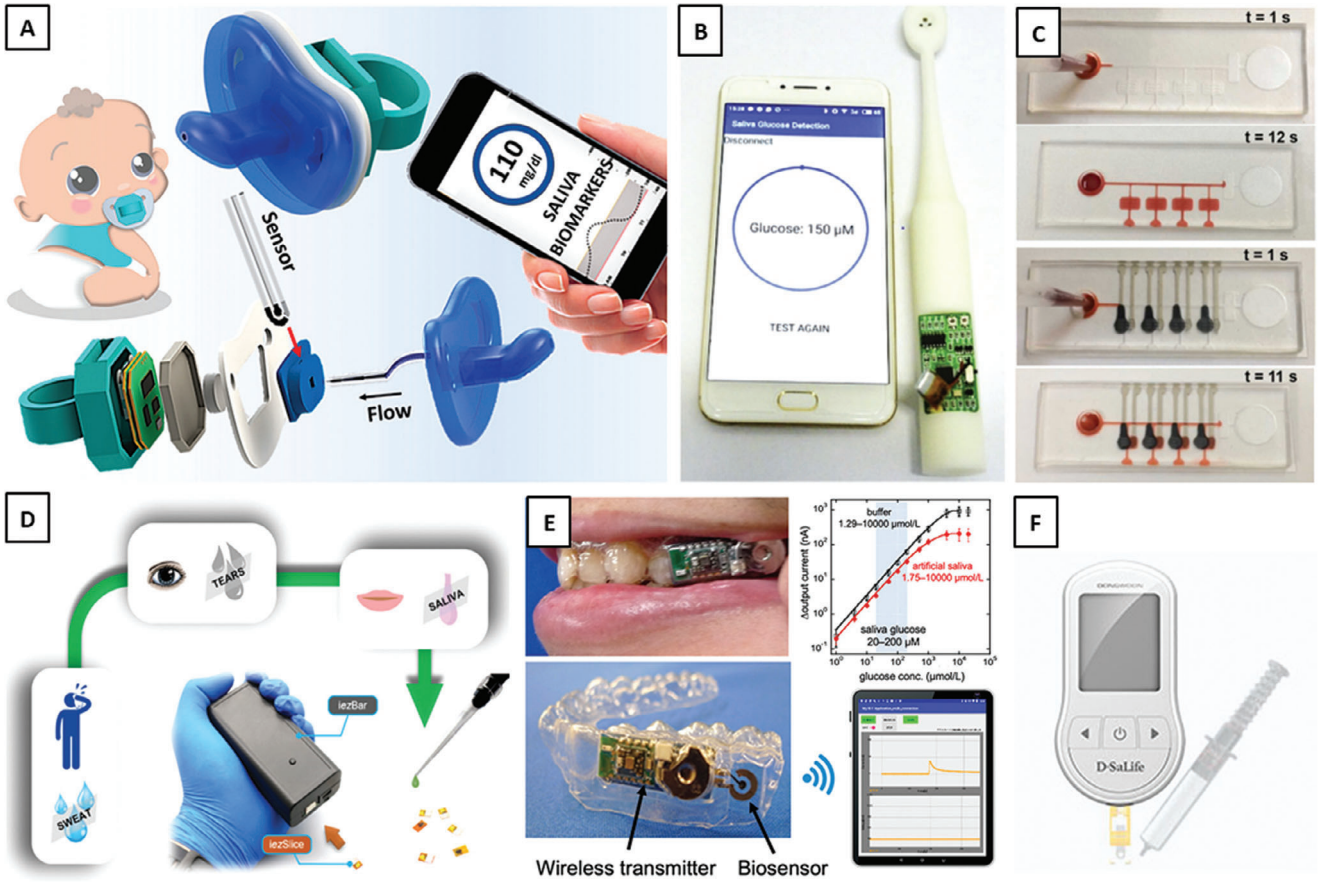

Figure 3. Salivary glucose sensor devices and microfluidic platforms. A) Fully integrated pacifier with PB/GOx-based sensor. Reproduced with permission.[55] Copyright 2024, American Chemical Society. B) Smart toothbrush with bronze-based sensor. Reproduced with permission.[64] Copyright 2024, Elsevier. C) Portable microfluidic sensor. Reproduced with permission.[77] Copyright 2024, Elsevier. D) Fully integrated system with point-of-care glucose monitoring. Reproduced with permission.[56] Copyright 2024, American Chemical Society. E) Mouthguard sensor integrated with a wireless module and battery. Reproduced with permission.[27] Copyright 2024, American Chemical Society. F) D-SaLife: salivary glucose sensor available in the market developed by Dongwoon Anatech. Reproduced with permission from Dongwoon Anatech.[82]

ringe containing an absorbent pad to collect saliva directly from their mouth, then apply a "drop" (i.e., 5 µL) onto the electrode inserted in the meter. Similarly, iQ Biozoom,[83] developed by iQ Global Group, utilizes an absorbent strip to collect the patient's saliva, which is then inserted into a digital meter housing the electronics. This device employs an enzymatic detection system.

4.6. Performance

The performances of the existing sensors analyzed in this review as specifically applied for salivary glucose detection, are illustrated in **Figure 4** for comparative analyses. The sensors are categorized into enzymatic and non-enzymatic types and their linear detection ranges are depicted as horizontal bars. Further, the glucose concentration in saliva for healthy people (green band) and diabetic patients (red band) are highlighted. Figure 4 illustrates a recent trend where research efforts have predominantly concentrated on non-enzymatic systems rather than enzymatic sensors. This shift is primarily motivated by the potential to overcome drawbacks associated with enzyme utilization, such as limited reproducibility and low stability.[5j] However, as shown in Figure 4, performances are not significantly different between enzymatic and non-enzymatic sensors, albeit being strongly materials- and design-dependent.

In terms of device shelf life, non-enzymatic sensors are often able to maintain signal loss lower than 10% for one month under ambient conditions,[61,68a,84] except for some cases where metal oxidation hinders sensor performance.[64] On the other hand, enzymatic sensors typically require storage at refrigerated temperatures (4 °C) and/or under vacuum to maintain their activity for up to 4 weeks.[57,58,85]

The complex composition of saliva represents a great barrier to salivary glucose sensor commercialization. The most common interferents studied have been ascorbic acid, uric acid, and dopamine, which are known electroactive molecules included in selectivity studies in amperometric sensors. However, proteins have been a major issue for most studies. In fact, the majority of the sensors developed report promising results only with artificial saliva,[60,86,87] usually composed of water, NaCl, KCl, $CaCl_2$, and $NaHCO_3$, or on centrifuged human saliva,[62,64,69a,84b,85] thus removing high molecular weight

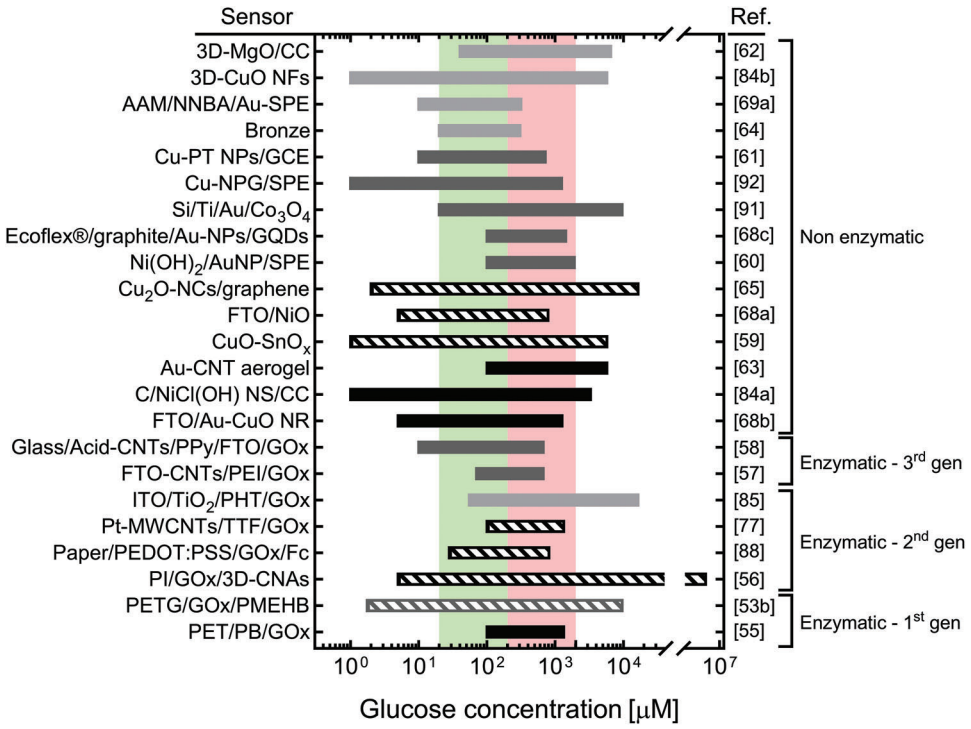

Figure 4. Linear detection ranges of the sensors referenced in this review. Sensor materials are reported on the left, while the type (enzymatic or non-enzymatic and generation) is shown on the right. The color of the bars indicates the sample tested: centrifuged human saliva (light grey), artificial saliva (dark grey), and human saliva (black). The line pattern in the bars indicates that membranes are adopted in the sensor. The colored shades indicate salivary glucose level ranges for healthy individuals (green: 10–200 μM) and diabetic patients (red: 200–2000 μM). These values are indicative only and are based on the data retrieved from published studies (see Table 4). Abbreviations: PETG, poly(ethylene terephthalate glycol); PMEHB, poly(MPC-co-EHMA-co-MBP); UA, uric acid; AA, ascorbic acid; PET, poly(ethylene terephthalate); PB, Prussian blue; SPE, screen-printed electrode; NQ, 1,4-naphtoquinone; PI, polyimide; CNA, carbon nanosphere network aerogel; PEDOT:PSS, poly(3,4-ethylenedioxythiophene) poly(styrene sulfonate); Fc, ferrocene; ITO, indium tin oxide; PHT, poly(3-hexylthiophene); MWCNT, multiwall carbon nanotubes; PU, polyurethane; PEG, poly(ethylene glycol); TTF, tetrathiafulvalene; FTO, fluorine tin oxide; CNT, carbon nanotube; PEI, polyethyleneimine; PPy, polypyrrole; NC, nanocube; NR, nanorods; AAM, acrylamide; NNMBA, N, N′-methylene bis-acrylamide; LA, lactic acid; NP, nanoparticle; GQD, graphene quantum dot; NF, nanoflake; NS, nanosheet; CC, carbon cloth; NPG, nonporous gold; GCE, glassy carbon electrode.

molecules, principally proteins.[88] These practices are common in saliva analysis studies, as they facilitate the detection of the target analyte by decreasing the number of interferents. Nevertheless, centrifugation would be prohibitive to carry out in POC settings, while sensors tested with artificial saliva need to be validated with actual human saliva. We note that aptamer-based FETs do not require separations due to their high selectivity, even against closely related molecules, and circumvention of the need for electrochemical detection.[31,53a,89]

Several sensors employed for the direct measurement of glucose in human saliva encountered limitations in covering a sufficiently wide concentration range, 20 to 1000 μM, due to interferences from large compounds such as proteins and cholesterol in saliva samples, especially non-enzymatic sensors, in which the absence of a selective enzyme could hinder the sensor performance. To mitigate this issue, membranes have been introduced to filter out these larger molecules, enabling the diffusion of glucose's smaller molecules to the sensor. Studies utilize materials such as Nafion,[59,68a,90] chitosan,[90] and cellulose acetate[53b] for this purpose. Other sensing techniques available have intrinsic selectivity and specificity in their sensing elements (e.g., aptamers), and would not face the same challenges.

Developing a sensor with a wide linear range for detecting glucose in human saliva has proven to be a formidable task. However, Chakraborty et al. overcame this challenge by designing a non-enzymatic system that utilized hydrothermally grown Au-decorated CuO nanorods on a fluorine-doped tin oxide-coated glass substrate.[68b] This approach resulted in a highly selective and stable sensor with a LOD of 0.17 μM. Likewise, Wang et al. achieved a linear detection range spanning from 1 to 3450 μM by employing a NiCl(OH) nanosheet array grown on a carbon cloth.[84a] Notably, both sensors exhibited the ability to detect glucose selectively in the presence of other analytes such as uric acid, ascorbic acid, dopamine, and fructose.

5. Future Perspectives and Challenges

Saliva glucose sensors, as documented in the literature, utilize a diverse range of materials and predominantly adopt two key detection strategies: enzymatic and non-enzymatic. Both types of sensors exhibit comparable performance in terms of sensitivity and detection range. However, a significant challenge for their practical implementation lies in the requirement of a substantial sample volume. In an effort to overcome this challenge, re-

searchers propose integrating these sensors into commonly used items for saliva collection, such as toothbrushes, mouthguards, and pacifiers. This approach facilitates the collection of larger saliva samples.[53b,55,64,75] Additionally, microfluidic systems and porous substrates such as paper, are viable strategies to reduce sample volume.[77] However, alongside sample reduction, efficient methods for direct saliva analysis are essential.

It is important to note that less than half of the reported sensors have been tested with actual human saliva. The complex composition of saliva poses a challenge for achieving selective and accurate detection. Beyond proteins, which may cause biofouling, other molecules of interest should be evaluated for selectivity. These include substances listed by the Food and Drug Administration (FDA) as potential interferents in blood glucose monitoring (i.e., acetaminophen, salicylic acid, tetracycline, dopamine, ephedrine, ibuprofen, levodopa, methyldopa, tolazamide, ascorbic acid, bilirubin, cholesterol, creatinine, triglycerides, and uric acid)[91] as well as sugars, especially galactose, mannose, and xylose.[92] Furthermore, considering the dynamic of the buccal cavity environment influenced by factors like eating, drinking, smoking, and oral hygiene products, studies should incorporate experiments that account for these confounding variables.[51]

Many studies addressing sensor performance have examined artificial saliva rather than human saliva to avoid the interference of other analytes. An alternative method involves saliva centrifugation to separate larger molecules (such as proteins) from this body fluid, thereby enhancing sensor sensitivity. While this centrifugation approach may not be suitable for point-of-care testing, membranes can be used efficiently to isolate larger molecules. This strategy mitigates the impact of interferents and enables selective detection of glucose in human saliva for POCTs. Among various materials, Nafion has been the preferred materials choice for such membranes. Although selective detection of glucose in human saliva is possible without membranes, as demonstrated by Nechilyl et al., Wang et al., and others, only two studies reported sensors able to detect glucose across the entire concentration range of interest.[68b,84a] Considering the prospective applications of saliva-based glucose sensors in healthcare, it is crucial to consider this detection range, ensuring suitability for both healthy individuals and those with diabetes, as illustrated in Figure 4.

Lastly, it is important to consider that, due to the significant impact of a variety of habits, such as eating, drinking, smoking, and oral hygiene routine, it is difficult to compare different studies that carried out tests with human saliva even when their sampling methods were specified (see Table 4). Intra-study differences are nonetheless significant. We thus note how a crucial aspect of rendering salivary glucose analysis clinically relevant is to standardize sampling (even more accurately than with blood glucose measurements). This step is required to ensure repeatability, accuracy, and significance of the data produced.

6. Conclusions and Prospects

Saliva holds promise as a bodily fluid for noninvasive glucose detection. Nevertheless, it presents challenges, such as limited sample volume, complex composition, and lower biomarker concentrations, compared to blood or ISF. Therefore, future studies should prioritize the development of a sensor integrated into a portable device design that minimizes sample volume without compromising detection range, covering the entire relevant span of concentrations in saliva. Evaluating detection performance using untreated human saliva is crucial, with membranes potentially playing key roles in enhancing selectivity and ensuring high sensitivity. Leveraging these approaches, considering current technological capabilities and achievable sensitivity, may bring devices closer to real-world applications and commercial viability.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

aptamer, bioelectronic, electrochemical, glucose, saliva, sensor

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