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Analysis of urine using electronic tongue towards non-invasive cancer diagnosis

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ABSTRACT

Electronic tongues (e-tongues) have been broadly employed in monitoring the quality of food, beverage, cosmetics, and pharmaceutical products, and in diagnosis of diseases, as the e-tongues can discriminate samples of high complexity, reduce interference of the matrix, offer rapid response. Compared to other analytical approaches using expensive and complex instrumentation as well as required sample preparation, the e-tongue is non-destructive, miniaturizable and on-site method with little or no preparation of samples. Even though e-tongues are successfully commercialized, their application in cancer diagnosis from urine samples is underestimated. In this review, we would like to highlight the various analytical techniques such as Raman spectroscopy, infrared spectroscopy, fluorescence spectroscopy, and electrochemical methods (potentiometry and voltammetry) used as e-tongues for urine analysis towards non-invasive cancer diagnosis. Besides, different machine learning approaches, for instance, supervised and unsupervised learning algorithms are introduced to analyze extracted chemical data. Finally, capabilities of e-tongues in distinguishing between patients diagnosed with cancer and healthy controls are highlighted.

1. Introduction to electronic tongue (e-tongue)

Biological sensory systems have evolved through millions of years standing out in versatility, performance and sensitivity (Untereiner et al., 2014; van Wassenbergh et al., 2015). The human tongue is equipped with receptors ranging from 2000-10,000 taste buds; each taste bud contains 50–100 taste cells which are responsible for the five basic tastes (sweet, bitter, salty, sour, and umami) (Roper, 1995). This structure allows the tongue to discriminate fluids containing thousands of substances such as wine (Nery, 2019; Quideau, 2017). When interacting with chemical substances, the taste cells generate a non-specific signal that can be used to indicate some characteristics or qualities of the sample being analyzed (Rodríguez-Méndez et al., 2010). The produced signal is then transmitted through the taste nerves to the brain, which is the central unit responsible for processing the incoming signal and recognizing the type of taste (Picó, 2012). Even though the taste buds situated on the tongue are not highly specific, they have a broad response (Freeman et al., 2017). Real time processing by the brain from the five senses - sight, hear, smell, touch and taste - remains well beyond the capability of artificial cognitive systems (Tarassenko and Denham, 2006). Despite their advantages, it is impossible to use biological

sensory systems in monitoring of industrial processes, analysis of distasteful, hazardous or toxic samples such as drugs, viruses, bacteria and pollutants (Shimizu et al., 2020). To overcome these challenges, bioinspired systems have been developed based on biological sensory systems' principles such as tactile sensors which are intended to imitate the skin, electronic eye, electronic nose that mimic the mammalian nose when interacting with odor molecules and electronic tongue (e-tongue), an analytical device inspired by biological taste systems (Valle, 2011) (see Fig. 1).

E-tongues, on the other hand, are capable of accomplishing quantitative and qualitative analysis of complex solutions (Podrazka et al., 2017; Vlasov et al., 2005). E-tongues consist of an array of non-selective, highly stable, and cross-sensitive sensors and a suitable pattern recognition algorithm (PARC) or chemometrics. Various types of signal transduction methods have been used to develop e-tongues ranging from optical, electrochemical, mass to thermal sensors (Bagnasco et al., 2014; Huynh and Kutner, 2015). For instance, infrared spectroscopy showed to be a promising technique in food quality (Beullens et al., 2006; Ferrand-Calmels et al., 2014), medical diagnosis (Backhaus et al., 2010; Liu et al., 2002), and forensics (Pereira et al., 2018; Wong et al., 2019). Raman spectroscopy has also been extensively explored in various fields

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such as food quality control (Richardson et al., 2019; Zhu et al., 2018), forensics (González-Rodríguez et al., 2011; Muehlethaler et al., 2011), and pharmaceutical analysis (Roggo et al., 2010; Vajna et al., 2011). Fluorescence spectroscopy was also investigated in water quality (Heibati et al., 2017; Sorensen et al., 2018), food quality (Becker et al., 2003; Christensen et al., 2003), and cosmetics (J. Nie et al., 2008; J.F. Nie et al., 2008). Electrochemical based e-tongues have also been examined in food quality (González-Rodríguez et al., 2011; Muehlethaler et al., 2011), forensics (García-Brejjo et al., 2013) and pharmaceutical analysis (Pein et al., 2015). Alternatively, bioelectronic tongue (bioe-tongue), in which an array of biosensors is used (Bachmann and Schmid, 1999), was proposed in the late 90's. The use of highly selective and specific biosensors can enhance the performance of the e-tongues while the other non-selective sensors diminish the effect of a complex and changing background of interfering compounds. These biosensors can be constructed using a wide range of bioreceptors comprising nucleic acids, aptamers, antibodies, cells and most importantly enzymes. The addition of enzymes not only speed up the sensor's response, but also offers additional kinetic data which can considerably enhance the performance of the e-tongue (Podrazka et al., 2017). Bioe-tongue has found applications in different areas such as food and beverage analysis, environmental monitoring, pharmaceutical analysis and disease diagnosis (Wasilewski et al., 2020).

The data produced by aforementioned analytical techniques is analyzed using chemometrics – the art of extracting relevant chemical information (Lavine and Workman, 2008). Chemometrics is regarded as a subset of the more general domain – machine learning (ML) and benefits from the various approaches and algorithms offered by ML (Torrione et al., 2014). Several ML algorithms have been applied for extracting maximum of information from chemical data. The choice of a ML algorithm relies on the objective of the study (clustering, classification, or prediction) (Moncayo et al., 2015), the number of data points and features, interpretability of the model, data format, linearity of data, training time, prediction time and memory requirements (Ramya, 2020). ML could be divided into (i) supervised (ii) and unsupervised learning.

Supervised learning offers a powerful approach by presenting the algorithm with example inputs and their desired classes (outputs) to build a general model that maps inputs to classes (Moncayo et al., 2015). Supervised learning methodology could also be split up into two subgroups: classification and regression. Linear regression analysis is usually employed in making predictions by way of finding mathematical relationships between quantitative variables. Linear regression is considered as one of the most primitive ML methodologies which are still broadly utilized (Talabis et al., 2015). A wide variety of linear

regression models include simple linear regression (SLR), multiple linear regression (MLR), principal component regression (PCR), partial least squares regression (PLSR), and support vector machine (SVM) (Yan and Ramasamy, 2019). Linear regression has been utilized in many applications, for examples, determination of the total polyphenols content in green tea (Chen et al., 2008), glucose, fructose, and sucrose in bayberry juice (Xie et al., 2009), prediction of microbial numbers on Atlantic salmon (Tito et al., 2012) and quantification of urea, creatinine, glucose, protein, and ketone in urine (Pezzaniti et al., 2001). Alternatively, nonlinear regression is a type of regression analysis in which experimental data are represented by a nonlinear function which is a combination of one or more independent variables and model parameters (Giddings and Ratkowsky, 1991). For instance, one of the nonlinear regression algorithms – neural network has the ability of learning complex nonlinear relationships from a training dataset. This ability makes it appropriate for pattern recognition problems involving the uncovering of convoluted tendencies in high-dimensional datasets (Guenther, 2001). Classification is established on a collection of formerly labeled inputs to generate a discrimination model capable of distinguishing between two or multiple classes. Classification is founded on the similarities and differences among individuals within the same and different classes, respectively, by means of discriminating a set of classes based on their measured features or variables. One of the main concerns encountered in classification is feature engineering, which deals with figuring out the most significant features. Over the past few decades, several classification algorithms have been developed, such as linear discriminant analysis (LDA), logistic regression (LR), partial least squares discriminant analysis (PLS-DA), naive Bayes, k-nearest neighbors (k-NN), artificial neural networks (ANNs), SVM, and decision tree algorithms (Subasi, 2020).

Unsupervised learning is an alternative approach to supervised learning, which provides no labels (outputs) to the machine learning algorithm. ML models based on unsupervised learning are more convoluted and time-consuming. This approach is based on uncovering hidden clusters or patterns through common similarities in its input data. Two widespread unsupervised learning methods are clustering and principal components analysis (PCA). Cluster analysis is utilized for revealing similarities between unlabeled and unclassified data points. The purpose of this approach is to unearth distinct clusters within a dataset where samples in the same cluster possess analogous characteristics to each other. Clustering methods comprise two main methods, for instance, k-means clustering (k-means) and hierarchical clustering (HC) (Talabis et al., 2015). Meanwhile, PCA is an unsupervised learning algorithm used to reduce the dimensions of a dataset while maintaining most of the relevant information. PCA converts interconnected variables

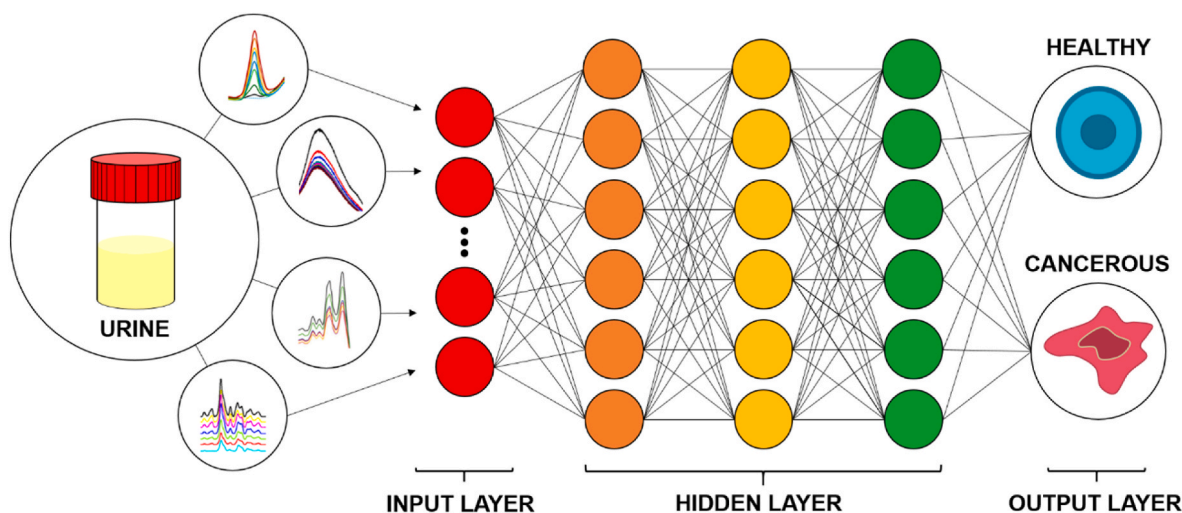


Fig. 1. Schematic of the non-invasive cancer prediction from urine using e-tongues.

into uncorrelated variables called principal components (PCs) while preserving most of the variation found in the original dataset. PCs are linear combinations of the original variables. The order of PCs is extremely important as the first few PCs explain almost all the variance present in a dataset (Roessner et al., 2011). Unsupervised ML techniques like PCA, HC, and k-means have been widely investigated in discriminating and correlating edible vegetable oils based on their physico-chemical properties (Herculano et al., 2021), detecting forensic documents fraud (Farid et al., 2021), and spotting the exposure of pregnant women to a variety of environmental chemical substances (Chen et al., 2021).

The aforementioned development of e-tongues has also led to several commercial products over the last few years. Firstly, the SA402B and TS-5000Z systems were developed by Insent Inc. (Atsugi-Shi, Japan) and are established on Toko's idea (Toko, 1996). Both instruments comprise potentiometric electrodes with lipid-polymeric membranes (Tahara and Toko, 2013). Another system known as α -Astree was built by AlphaMOS (Toulouse, France), consisting of seven ion-selective field effect transistors (ISFET). McScience Inc. (Suwon, Korea) also constructed a sensor array based on selective polyvinyl chloride and polyurethane membranes for H^+ , Na^+ , K^+ , Ca^{2+} , NH_4^+ , NO_3^- , Cl^- (Ciosek and Wróblewski, 2007a). These e-tongues have found extensive applications in food quality (Cui et al., 2013; Zhang et al., 2015), pharmaceutical analysis (Choi et al., 2015; Nakamura et al., 2015), and process monitoring (Jambrak et al., 2017; Yan et al., 2017). Importantly, e-tongue systems have been applied in cancer diagnosis, for instance, in examining several biological fluids such as serum (Lin et al., 2011; Pichardo-Molina et al., 2007), plasma (Feng et al., 2010, 2011), blood (Kalaivani et al., 2008), bile (Untereiner et al., 2014) and sputum (Lewis et al., 2010; Menzies et al., 2014) samples. In addition, portable optical e-tongues in the form of handheld systems were built by various companies including BWTEK, Rikagu Analytical Devices, Metrohm, Agilent in the last few decades. These point-of-care diagnostics (POCD) devices can be defined as rapid acquisition of medical tests at or near the patient site in order to achieve effective treatment in the shortest possible time (Ayatollahi, 2021). Today, health-care systems may well be better than in the past, but they still have several drawbacks, including (i) consumption of extensive financial resources, (ii) inconvenience or sometimes inaccessibility to large proportions of the population, particularly those in rural areas and developing countries and (iii) struggle in detecting diseases at early stages due to limited health status screening. The World Health Organization (WHO) suggested the establishment of e-Health systems and set e-Health as a major priority (WHO, 2018). E-Health can be described as the implementation of information communication technologies (ICTs) in the health care sector. It offers health care services where distance is a critical factor, with the aim of exchanging data to improve patients' management, diagnosis and monitoring (Rodrigues et al., 2016). Unlike conventional medical testing devices, e-tongues can be considered as e-Health diagnostic devices because of their minimal user involvement, low-cost, ability to analyze raw biological samples and manage and monitor patient health conditions in underserved area (Christodouleas et al., 2018). Such approach makes e-tongues promising for future e-Health systems allowing them to achieve efficient real-time online-based detection of diseases with the help of ML, big data and Internet of things (IoT) technologies (Kumar and Panda, 2022).

2. Analysis of urine using e-tongues for cancer diagnosis

Cancer is a large group of diseases comprising more than 100 different and unique diseases. Even though there are various types of cancer, they all involve uncontrollable and abnormal cell growth. Naturally, normal cells grow and split in a regulated way to deliver healthier cells and maintain the body's health. They could also get replaced with new cells when they become old or damaged. Unlike normal cells, cancerous cells continue to grow and produce new anomalous cells. They could also grow in an uncontrolled way and form

a mass of tissue (tumor) or invade other organs (metastases) (Mittra et al., 2018). According to the WHO, cancer is the second leading cause of death. In 2020, cancer accounted for approximately 9.9 million deaths. The deadliest cancer types were lung (2.21 million deaths), liver (830000) and stomach cancers (769000). Whereas, the most widely diagnosed cancer types were breast cancer (2.26 million cases), lung (2.21) and prostate cancers (1.41) (Ferlay et al., 2021).

Common cancer risk factors include age, obesity, physical inactivity, excessive red and processed meat consumption, alcohol, tobacco smoking, family history, and air pollution. Modifying or avoiding these risk factors could prevent 30%–50% of cancer deaths. The mortality rate can also be reduced through existing prevention strategies and early detection (Akhtar and Bansal, 2017; Makhoul, 2018; Yu et al., 2018). Cancer detection could be achieved through physical examination, laboratory tests, imaging, or biopsy. Physical examination has often been used for cancer detection using palpation to look for lumps, differences in skin color, or swelling of an organ. However, physical examination has several drawbacks, such as expertise and skills of the examiner, non-objective findings, lack of reproducibility, many false negatives, and incapability of spotting non-palpable cancers (Foster, 1994; Morimoto et al., 1993). Clinical tests are also used to diagnose cancer; these tests are based on urine or blood analysis which may help pinpoint anomalies that can be triggered by cancer (Sharma, 2009). Cancer prognosis and diagnosis could also be attained using a large variety of imaging techniques including mammography, ultrasound, Doppler imaging, computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), microwave imaging, and their variations and combinations. These techniques allow cancer detection through an examination of bones and internal organs (Hayat, 2008). However, they present several disadvantages such as high cost, radiation exposure, long acquisition time, low spatial resolution, cannot be used for whole-body imaging, limited tissue depth penetration, and poor soft-tissue contrast (Sivasubramanian et al., 2014). A biopsy is considered as the only definite approach to identify cancer since it involves collecting cells and their analysis in a microscope to look for dissimilarities between normal and cancerous cells. These differences could be observed in the form of non-uniformity, cells size, and organization (Woods and Reichart, 2017). Nevertheless, tissue collection is unsafe, painful, and unpleasant for the patient and sometimes is inaccessible. Additionally, solid biopsy is costly, time-consuming, and non-repeatable (Marrugo-Ramírez et al., 2018). Hence, an urgent demand for non-invasive, portable, and low-cost cancer diagnosis methods.

Urine is a transparent, sterile and amber-colored biological fluid formed using filtration, reabsorption, and tubular secretion from the kidney. It contains more than 95% of water, inorganic salts (chloride, sodium and potassium), and small soluble organic molecules such as urea (most abundant organic metabolite found in urine), hydroxy acids and derivatives (like citric acid), ammonia, creatinine, hippuric acid, amino acids and derivatives, carbohydrates and carbohydrate conjugates (Bouatra et al., 2013; Sensabaugh, 2015; Zhang et al., 2020) which are present due to two pharmacokinetic processes (metabolism and excretion). In short, these endogenous molecules are converted into more water-soluble molecules under a process named metabolism prior to their excretion into urine (Saghir, 2019). The diverse and rich urine composition in patients diagnosed with cancer may help unravel novel cancer biomarkers that could be useful in cancer prognosis and diagnosis (Sadana and Sadana, 2015). Even though blood analysis has now replaced numerous urine tests in clinical laboratories, urinalysis still presents some advantages, including (a) convenient collection, especially for screening uses, (b) high concentration of metabolites comparing to blood, which ease their detection (c) unnecessary of sample preparation before urinalysis as it is often free of interfering molecules like lipids and proteins compared to blood (d) physical characteristics of urine such as volume, color, turbidity or smell. Abnormalities in these characteristics may designate disease or metabolic imbalances

(Challand and Jones, 1994). By using e-tongue, this review provides a perspective on cancer diagnosis from urine in non-invasive, portable, and low-cost manner. Therefore, nuclear magnetic resonance (NMR) and mass spectrometry (MS) based e-tongues are excluded from the review due to expensive instrumentation, complex sample pre-treatment, and well-qualified technicians. Herein, the focus are spectroscopic (Raman, infrared, and fluorescence) and electroanalytical (potentiometry and voltammetry) techniques, which present little to no sample preparation, fast, non-destructive, and on-site analysis, and miniaturization.

2.1. Raman spectroscopy

Raman spectroscopy is an attractive analytical technique that extracts chemical information by investigating individual chemical bond vibrations of molecules. This technique employs the inelastic scattering of light to generate Raman spectra (Old et al., 2014). As soon as light interacts with a molecule, a portion of the light is scattered with an identical wavelength as the incident light. This phenomenon is well

known as Rayleigh scattering. The intensity of this scattering varies strongly with wavelength. However, a significantly smaller fraction of light will reveal a minor shift in wavelength (about 10^{-6} of the original light) due to the interaction between the vibrating bonds and the incident photons. The wavelength of the scattered photons can be higher or lower wavelength comparing to that of the incident light. These wavelength shifts are recognized as Stokes and anti-Stokes, respectively, and establish the core of Raman spectroscopy (Klopprogge, 2016). Raman spectroscopy is a non-destructive and non-invasive technique that does not necessitate any sample preparation. Raman spectra have characteristic peaks specific to chemical bonds in the sample, and their intensities are proportional to the concentration of the analyte being analyzed (Giridhar et al., 2017). Raman spectroscopy's tolerance to water due to the weak Raman signal of water molecules –OH vibrational modes makes it suitable for analyzing water-containing samples with biological origins (Çulha, 2015). The range of applications of Raman spectroscopy extends from crucial biomolecules such as lipids, proteins, nucleic acids, and carbohydrates to body fluids, including urine, cell cultures, and tissue samples. Raman spectroscopy produces a unique

Table 1

Summary of e-tongues based on electroanalytical (potentiometry and voltammetry) and spectroscopic (Raman, infrared and fluorescence) methods for cancer diagnosis from urine.

Method	Cancer	Algorithm	Accuracy	Sensitivity	Specificity	Reference
Raman spectroscopy	Cervical	LDA	100%	100%	100%	Pappu et al. (2017)
Raman spectroscopy	Adenocarcinoma	GA-QDA	95.6%	94.4%	100%	Maitra et al. (2020)
Raman spectroscopy	Oral	PCA-LDA	75%	80%	70%	Brindha et al. (2016)
Raman spectroscopy	Oral	PCA-LDA	90.9%	86.3%	92.9%	Elumalai et al. (2015)
Raman spectroscopy	Oral	PCA-LDA	93.7%	98.6%	87.1%	Brindha et al. (2017)
Raman spectroscopy	Oral	PCA-LDA	93.7%	98.6%	87.1%	Elumalai et al. (2014)
Raman spectroscopy	Breast	PCA-LDA	91% (concentrated urine, tumor groups)	N/A	N/A	Bhattacharjee et al. (2015)
Raman spectroscopy	Bladder	PCA, -LDA, -DFA and -ANN	N/A	100%	100%	Kerr et al. (2014)
SERS	Breast	PCA-LDA	88%	81%	95%	Moisoiu et al. (2019)
SERS	Prostate	GA-PLS-LDA	86.6%	86%	87.1%	Ma et al. (2020)
SERS	Prostate	PCA-LDA	95%	100%	89%	Mistro et al. (2015)
SERS	Prostate and bladder	PCA-LDA	89%	N/A	N/A	Cui et al. (2020)
SERS	Esophagus	PCA-LDA	82.05%	72.3%	96.8%	Huang et al. (2014b)
SERS	Esophagus	PCA-LDA	86.3%	89.3%	83.3%	Huang et al. (2014a)
SERS	Nasopharyngeal and esophageal	PLS-DA	96.7%	93.5%	100%	Feng et al. (2017)
Infrared spectroscopy (FEWS ATR-FTIR)	Bladder	PLSDA _{BM} , PLSDA _J , PLSDA _B	82.35%	83.3%	87.5%	Bensaid et al. (2017)
Infrared spectroscopy (ATR-FTIR)	Esophageal	PCA-QDA	100%	100%	100%	Maitra et al. (2019)
Infrared spectroscopy (ATR-FTIR)	Prostate	PCA-LDA	N/A	83%	60%	Yap et al. (2019)
Infrared micro-spectroscopy	Bladder	PCA	N/A	N/A	N/A	Bird et al. (2008)
Infrared spectroscopy	Bladder	PCA	N/A	N/A	N/A	Gok et al. (2016)
Infrared spectroscopy (ATR-FTIR)	Endometrial and ovarian	PLS-DA, PCA-SVM (best model) and GA-LDA	Endometrial (95%), Ovarian (100%)	Endometrial (95%), Ovarian (100%)	Endometrial (100%), Ovarian (96.3%)	Paraskevaïdi et al. (2018)
Fluorescence (emission spectra and Stokes shift spectra)	Cervical	SLDA	82%	80%	78%	Masilamani et al. (2012)
Fluorescence (emission spectra and Stokes shift spectra)	Breast, cervical, colon, leukemia, esophagus, liver and bladder	DCA	86.7%	76%	92%	Masilamani et al. (2010)
Fluorescence (excitation emission matrices)	Head and neck, breast and cervical cancer	SLDA	94%	95%	94.4%	Rajasekaran et al. (2013)
Fluorescence (laser confocal microscopy)	Bladder	Naive Bayes	N/A	93%	100%	Fu et al. (2007)
Fluorescence (photo-bleaching)	Oral	NMC	82%	78%	86%	Dutta et al. (2019)
Potentiometry	Prostate	PCA, SIMCA, PLS-DA, RF and LR	(LR) 93%	100%	93%	Solovieva et al. (2019)
Voltammetry	Bladder	AHC	N/A	N/A	N/A	Doménech-Carbó et al. (2018)
Voltammetry	Prostate	PLS-DA	N/A	91%	73%	Pascual et al. (2016)
Potentiometry	Bladder	FPB-NN, PLS-DA	92.2%	N/A	N/A	Lvova et al. (2009)

fingerprint based on the various components found in biological samples.

Raman analysis of biological fluids is often difficult due to the complexity of samples. Raman spectra from biological fluids such as urine, blood, and saliva are dense and comprise various biomolecules. Moreover, the differences between healthy and cancer samples are very small and hard to detect in raw spectra. Therefore, data processing of these complex spectra can help obtain meaningful information for diagnosing cancer (Gautam et al., 2015; Kuhar et al., 2018). Numerous studies have shown the ability of Raman spectroscopy and ML to discriminate urine samples of patients diagnosed with cancer and healthy controls with high accuracy, specificity, and sensitivity.

Raman spectroscopy has been implemented in studies involving the detection of different types of cancers. Raman spectroscopy was utilized by (Bhattacharjee et al., 2015) for preliminary breast cancer diagnosis on animal models in combination with PCA-LDA. This approach led to classification efficiencies of 80% and 72% using unprocessed urine and 78% and 91% using concentrated urine for controls (C) (obtained by vacuum dehydration) and breast tumor-bearing rats (T), respectively (Table 1). Moreover, the discrimination was achieved between urine samples collected from prior breast tumor development (TT) in rats and rats that did not develop tumors despite carcinogen treatment (NTT). Concentrated urine of NTT rats could be classified as 'normal' (C or NTT) with ~83% efficiency, whereas concentrated urine from visibly and palpably normal rats that eventually developed tumor (TT rats) could be classified as 'abnormal' (TT or T) with ~72.5% efficiency (Table 1).

In cancer diagnosis of human samples, (Pappu et al., 2017) employed Raman spectroscopy and LDA to discriminate between patients diagnosed with cervical cancer and healthy controls from urine samples. LDA was utilized to analyze the Raman spectra, and the established model achieved an accuracy of 100% for cervical cancer detection (Table 1). Raman spectroscopy and genetic algorithm quadratic discriminant analysis (GA-QDA) were utilized by (Maitra et al., 2020) to distinguish normal, squamous epithelium, inflammatory, Barrett's, low-grade dysplasia, high-grade dysplasia and esophageal adenocarcinoma from plasma, serum, saliva, and urine. The model accomplished 100% discrimination for all saliva and urine samples categories using only 16 wavenumbers (Table 1). Raman spectroscopy was also used by (Brindha et al., 2016) to discriminate oral malignant patients and healthy volunteers ($n = 10$) from blood, saliva, and urine samples using PCA-LDA. This approach led to classification models with similar results for blood, saliva, and urine (accuracy 75%, specificity 80%, and sensitivity 70%) (Table 1). To obtain higher accuracy, sensitivity, and specificity, a higher number of patients ($n = 121$) has been used (Elumalai et al., 2015) (Kumar and Sharma, 2018) to diagnose oral cancer and healthy controls as the number of samples is important for obtaining accurate and reliable results. The same approach has been used by (Elumalai et al., 2014) to differentiate normal and oral cancer subjects ($n = 167$), leading to a classification model with a sensitivity and specificity of 98.6% and 87.1%, respectively, and overall accuracy of 93.7% (Table 1).

Even though low- and high-wavenumber Raman spectroscopy showed a good classification accuracy for the diagnosis of oral cancer (Brindha et al., 2017), the high-wavenumber (of 2600–3500 cm^{-1}) had shown a slight advantage over the fingerprint region to discriminate urine samples from normal subjects, oral premalignant and malignant patients ($n = 80$). Discriminant analysis was performed using PCA-LDA across normal and oral premalignant, normal and oral malignant, and between the three groups. The diagnostic accuracy was 94.9%, 92.1%, and 89.1%, respectively (Table 1). Urinary metabolites such as flavoproteins, tryptophan, and phenylalanine were responsible for the spectral differences between these three groups. In another study, classification sensitivity and specificity of the e-tongue in urine analysis of bladder cancer cells can be optimized by excitation wavelengths and sample substrates (Kerr et al., 2014). The results confirmed that the excitation wavelength of 473 nm surpasses that of 532 nm, while the

glass and fused silica gave comparable and consistent results comparing to calcium fluoride. This study also showed that the combination of ANN and discriminant function analysis (DFA) with PCA achieved the best results.

The cross-section of Raman scattering is extremely small, leading to very low scattering efficiency and therefore limiting its sensitivity. However, the weak Raman signal can be significantly enhanced using surface-enhanced Raman spectroscopy (SERS). SERS was unintentionally discovered by (Fleischmann et al., 1974) when they attempted to perform Raman analysis using pyridine (Py) on a roughened silver (Ag) electrode to produce a high surface area on the roughened metal surface. Surprisingly, the quality of the acquired Raman spectra was very high. Therefore, assuming that the increase of the surface area mainly triggers the increase of the Raman intensity. Nevertheless (Albrecht and Creighton, 1977; Jeanmaire and Van Duyne, 1977), comprehended that the rise of the surface area is not the main reason for the Raman enhancement until (Jeanmaire and Van Duyne, 1977) suggested that an electromagnetic effect is responsible for this enhancement. Their proposition is based on the excitation of localized surface plasmons, while (Albrecht and Creighton, 1977) advocated that it is mainly due to a charge transfer effect of the adsorbed molecule on the metal surface. It is still challenging to separate these two effects experimentally, and the precise mechanism of the enhancement effect of SERS is still a matter of controversy in the literature (Sur, 2010). Nevertheless, SERS has been proven as a novel e-tongue for urine screening of breast, bladder, esophagus, nasopharyngeal, and prostate cancers (Cui et al., 2020; Feng et al., 2017; Huang et al., 2014a, 2014b; Ma et al., 2020; Mistro et al., 2015; Moisoiu et al., 2019) using silver nanoparticles (AgNP) and gold nanoparticles (AuNP) as SERS substrates. Various algorithms such as PCA-LDA, genetic algorithms partial least squares linear discriminant analysis (GA-PLS-LDA), and PLS-DA have been used to discriminate urine of cancer patients from that of healthy controls. All models achieved a sensitivity of >81%, a specificity of >97%, and overall accuracy of >86% (Table 1). It is worth mentioning that urinary modified nucleosides are degradation products of nucleic acids and are a typical tumor marker for different cancer types presented in human urine (Schram, 1998). Therefore, their usage led to better results compared to raw urine samples suggesting that the combination of urinary modified nucleosides, SERS, and PLS-DA is powerful for the clinical diagnosis of esophageal and nasopharyngeal cancer.

2.2. Infrared spectroscopy

Nearly all chemical vibrations arise at the infrared region's energy levels and produce a distinctive vibrational fingerprint. Chemical vibrations are visible in the infrared regions as long as there is a change in the molecule's dipole moment (Haris and Chapman, 1992). Such vibrations can be visualized using a spectrum of wavenumbers usually measured in the mid-infrared range (4000–400 cm^{-1}) (Lewis et al., 2010; Panikuttira and O'donnell, 2018). Consequently, the infrared spectrum is constructed throughout the measurement of the absorbed and transmitted light after passing through a sample. In the case of biological samples, the resulting infrared spectrum is convoluted due to the large number and size of molecules present in the sample. Infrared spectroscopy presents numerous advantages, including a non-invasiveness, wide variety of applications, minimal preparation and amount of sample, short acquisition time (Barth, 2007). When working with tissue samples, infrared spectroscopy is advantageous as infrared spectra normally have a higher signal-to-noise ratio than Raman spectra (Kendall et al., 2009). Nevertheless, it is quite challenging to use infrared spectroscopy in vivo applications since most biological samples contain a high water content, as water is extremely absorptive in infrared spectroscopy (Kendall et al., 2009; Mackanos and Contag, 2010).

In combination with ML, infrared spectroscopy has been widely used in diagnosing ovarian, breast, colorectal, oral, and lung cancers from

different biological samples, including blood serum, plasma and saliva (Backhaus et al., 2010; Barlev et al., 2016; Bel'skaya et al., 2019; Ferreira et al., 2020; Gajjar et al., 2013; Zlotogorski-Hurvitz et al., 2019). (Bird et al., 2008; Gok et al., 2016) reported an automatic method for bladder cancer screening from cells found in human urine. Infrared spectroscopy and PCA revealed distinct spectral classes which correlate with visual cytology and cystoscopy. Both techniques reached satisfactory results in clustering bladder cancer patients and healthy controls. Whereas (Bensaid et al., 2017) used a new system based on fiber-optic evanescent wave spectroscopy (FEWS) technology to acquire spectra from voided urine and bladder wash samples from bladder cancer patients and healthy controls. PLS-DA was used with three new rules Bayesian (PLSDA_B), joint (PLSDA_J), and best model (PLSDA_{BM}). A comparative study with SVM and k-means clustering was conducted, and an optimal accuracy was achieved by joint PLS-DA_J and best model PLS-DA_{BM} (82.35%) (Table 1). The proposed statistical methods were implemented in an e-tongue that is very encouraging in automatic bladder cancer detection.

(Maitra et al., 2019) used infrared spectra acquired from urine, plasma, saliva, and serum to discriminate between four different classes of esophageal disease: Barrett's, inflammation, high-grade dysplasia, low-grade dysplasia, and esophageal adenocarcinoma. The GA-QDA model achieved 100% accuracy (Table 1), specificity, and sensitivity using the urine dataset. The same results were achieved by (Maitra et al., 2020) when using Raman spectroscopy. Both techniques showed promising results for esophageal cancer discrimination.

Additionally (Paraskevaidi et al., 2018), used attenuated total reflectance infrared spectroscopy (ATR-FTIR) to discriminate between endometrial and ovarian cancer patients and healthy volunteers from urine samples using multivariate classification algorithms. PLS-DA, PCA-SVM, and GA-LDA approach led to classification models with different sensitivity, accuracy, and specificity of which PCA-SVM achieved high levels of accuracy for both endometrial and ovarian cancer (Table 1). In addition to this (Yap et al., 2019) implemented ATR-FTIR to investigate urine extracellular vesicles as potential biomarkers for prostate cancer detection. Preliminary results of a PCA-LDA model performed on a small dataset (11 patients) showed a potential development of an ATR-FTIR diagnostic approach for prostate cancer. The model achieved a sensitivity of 83% and a specificity of 60% (Table 1).

2.3. Fluorescence spectroscopy

Fluorescence spectroscopy is a strong and efficient technique to explore the chemical and physical characteristics of molecules. The Jablonski diagram suggests a useful explanation of the relevant transitions and excited states. The excitation process is initiated by a fast transition from the ground state to the excited state. Following excitation, the compound is rapidly relaxed to its lowest vibrational level of the excited electronic state. The process of vibrational relaxation happens on a timescale of femtoseconds to picoseconds. Fluorescence emission occurs as soon as the fluorophore decays from the singlet excited state to a permissible vibrational level in the ground state. The fluorescence emission and excitation spectra indicate the vibrational levels in the ground and the excited states, respectively (Lakowicz, 2006).

The key advantage of fluorescence spectroscopy is its high sensitivity (10–100 folds compared to UV-VIS spectroscopy) and its capability to quantify traces of fluorophores using a very low amount of sample. This high sensitivity makes fluorescence one of the best existing techniques for trace analysis (Itagaki, 2000). Fluorescence spectroscopy is an effective tool broadly utilized for medical, forensic, genetic, and biotechnological applications to obtain quantitative and qualitative information (Chirayil et al., 2017). Thus, several fluorescence-based e-tongues have been applied for cancer diagnosis through urine, e.g. in cervical cancer diagnosis (Masilamani et al., 2010, 2012). The fluorescence emission spectra (FES) and Stokes shift spectra (SSS) are

analyzed to discriminate urine and blood samples of cervical cancer patients against those of breast, colon, leukemia, esophagus, liver and bladder cancer patients and healthy controls (Table 1). This technique showed that the relative fluorescence intensities of porphyrin, flavin, NADH, and collagen are distinctly different in cervical cancer patients. Not only fluorescence intensity but also the fluorescence excitation-emission matrices (EEM) have been used to discriminate between patients diagnosed with head and neck, breast, and cervical cancer from healthy controls (Rajasekaran et al., 2013). EEM is a three-dimensional matrix consisting of an excitation-emission-intensity spectrum. This technique is rapid, selective, and highly sensitive. It can acquire a large amount of data by simultaneously varying the emission and excitation wavelengths (Heidari et al., 2018). EEMs were used as an input for stepwise linear discriminant analysis (SLDA), leading to a classification model with a sensitivity, specificity, and overall accuracy of 95%, 94.4%, and 94%, respectively (Table 1).

Fluorescence cytology of urine was also capable of detecting bladder cancer (Fu et al., 2007). Urinary cells were extracted and incubated with a novel photosensitizer called hypericin to improve the fluorescence contrast between healthy and cancerous cells, and laser confocal microscopy (LCM) was used to capture fluorescence images. Bayes classifier was applied on the fluorescence images, leading to a discrimination model with 93% and 100% sensitivity and specificity, respectively (Table 1) and outperforming urine cytology in discriminating benign and low-grade tumor (sensitivity of 87% and specificity of 40%). Further (Dutta et al., 2019), used fluorescence photo-bleaching of human urine samples to evaluate its ability to discriminate between oral cancer patients and healthy volunteers. The spectral differences between oral patients and healthy volunteers were attributed to flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NADH) and porphyrins. Photo-bleaching constants were explored by a near mean classifier (NMC) based algorithm using leave-one-out cross-validation. The NMC model achieved an overall accuracy of 82%, sensitivity of 78% and a specificity of 86% in classifying the two classes of urine samples and showing the potential of photo-bleaching as an alternative approach for oral cancer diagnosis (Table 1).

2.4. Electrochemistry

Electrochemical tongues are one of the most common approaches for chemical analysis by monitoring electrochemical signals of a working electrode responsive to the change of the analyte concentration (Ciosek et al., 2006; Ciosek and Wróblewski, 2007b; del Valle, 2010). According to their operation mode, sensor array of electrochemical tongues can be divided into four categories: potentiometric, voltammetric/ampereometric, conductometric, and impedimetric sensors (Fraden, 2010).

Potentiometric sensors are established on measuring the potential between a reference electrode and a working electrode at zero current or with a small anodic or cathodic current applied to the indicator electrode (Allen, 2010). The potential of the reference electrode is constant during measurement, while that of the working electrode varies with the concentration of the analyte (Isildak and Özbek, 2020). At zero current, the potential-current formula can be written in the form of the Nernst equation, which oversees almost every operation in potentiometric sensors (Janata and Janata, 2009a). Potentiometric sensors are non-destructive, selective, low cost, easy to fabricate, and their mode of operation is well-studied. However, their potential measurements are affected by temperature, deactivation of the sensing surface due to the adsorption on the working electrode, precipitation, or corrosion (Miró and Frenzel, 2019). These sensors are widely found in electrochemical tongues and used in various fields and applications (Śliwińska et al., 2014). However, their application in cancer diagnosis from urine is very scarce. Solovieva et al. (2019) used a potentiometric e-tongue containing twenty-eight sensors to distinguish urine samples obtained from prostate cancer patients and healthy volunteers using different ML algorithms (PCA, SIMCA, PLS-DA, RF, and LR). Following variable

selection, an optimized sensor set containing nineteen sensors and logistic regression allowed constructing a classification model with 100% sensitivity, 97% accuracy, and 93% specificity (Table 1). On the other hand (Lvova et al., 2009) reported a potentiometric e-tongue containing metallic sensors and ion-selective electrodes with PVC solvent polymeric membranes. The e-tongue with dedicated sensors distinguished bladder cancer samples from the controls using PLS-DA and forward back-propagation neural networks.

Voltammetric and amperometric sensors are focused on measuring the electrical current generated throughout a redox reaction. The information is extracted from the relationship between the generated current and the concentration of the analyte (Janata and Janata, 2009b). Amperometric sensors are based on a constant potential, while the applied potential in the case of voltammetric sensors is varied. A three-electrode system comprising a working, a counter, and a reference electrode, is usually employed in these sensors, although a two-electrode system can also be utilized. The main advantage of a three-electrode system is its ability to apply and monitor the potential through the reference electrode accurately and measure the current by way of the counter electrode (Zhang and Hoshino, 2019). (Pascual et al., 2016) demonstrated the use of a simple voltammetric e-tongue based on metallic electrodes and PLS-DA. This method discriminated between urine samples from patients with prostate cancer and non-cancer urine samples (patients after radical prostatectomy and patients diagnosed with BPH) with a sensitivity of 91% and a specificity of 73% (Table 1). Direct electrochemical analysis of urine was also performed by (Doménech-Carbó et al., 2018) using a dual voltammetric sensor array based on gold and glassy carbon electrodes and ascendant hierarchical classification (AHC) to cluster urine samples obtained from bladder cancer patients and healthy controls. The obtained voltammetric profiles for urine displayed significant differences using AHC as a pattern recognition algorithm.

3. Conclusion and future trends

E-tongues have shown great potential in dealing with complex biological fluids and reducing their interfering effect. E-tongue systems offer rapid, little-to-no-sample preparation, non-destructive, miniaturization, and on-site capabilities, unlike other expensive and time-consuming analytical techniques. In this review, the authors reported e-tongues developed for solving difficult and increasing challenges related to early cancer diagnosis. Table 1 exhibits the list of cancers diagnosed by e-tongues and bladder and prostate cancers are the two focus type of cancers. Different spectroscopic and electrochemical techniques (Table 1) have been used as e-tongues. They have shown remarkable capabilities to discriminate urine samples of the cancer patients from those of healthy individuals. The review also showed that bladder cancer, prostate, oral, cervical, and breast cancer are the most widely studied cancer types by e-tongues. Among techniques, Raman and SERS have been broadly employed in non-invasive cancer diagnosis from urine compared to the other analytical techniques due to their prominent usage in chemical analysis of biological fluids, rich chemical information and non-invasiveness. Hence, its widely use in cancer screening, diagnosis, and intraoperative surgical guidance in the past ten years (Cui et al., 2018). In addition, innovation in data collection and pattern recognition algorithms of the e-tongues (e.g. PCA-LDA and PLS-DA) have displayed good classification efficiencies.

Previous studies focused more on invasive biological fluids such as blood and serum, while non-invasive study with urine offers comparable diagnostic capabilities. However, a relatively lower number of samples knowing that the size of data highly impacts the quality of the mapping function and performance of the model. Furthermore, the complexity of the data and the problem suggests using advanced signal analysis algorithms compared to the ones used in these studies. Lastly, the literature about the development of point-of-care devices is very scarce. Therefore, we believe that more studies of e-tongues related to different

kind of cancer types, large number of patients, point-of-care or lab-on-a-chip device (Daikuzono et al., 2015; Kumar and Panda, 2022), and more advanced ML algorithms such as boosting algorithms (Gradient Boost, AdaBoost, XGBoost and CatBoost) and neural networks, are absolutely essential for bringing them closer to consumers as portable and low-cost early cancer diagnosis devices.

Credit author statement

M. Zniber: idea and writing - original draft, **P. Vahdatiyekta:** writing-reviewing, **T.-P. Huynh:** idea and writing-reviewing and editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

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