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All-MXene electronic tongue for neurotransmitters detection

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ABSTRACT

Neurotransmitters (NTs) are molecules produced by neurons that act as the body's chemical messengers. Their abnormal levels in the human system have been associated with many disorders and neurodegenerative diseases, which makes the monitoring of NTs fundamentally important. Specifically for clinical analysis and understanding of brain behavior, simultaneous detection of NTs at low levels quickly and reliably is imperative for disease prevention and early diagnosis. However, the methods currently employed are usually invasive or inappropriate for multiple NTs detection. Herein, we developed a MXene-based impedimetric electronic tongue (e-tongue) for sensitive NT monitoring, using Nb_2C, Nb_4C_3, Mo_2C, and $Mo_2Ti_2C_3$ MXenes as sensing units of the e-tongue, and Principal Component Analysis (PCA) as the data treatment method. The high specific surface area, distinct electrical properties, and chemical stability of the MXenes gave rise to high sensitivity and good reproducibility of the sensor array toward NT detection. Specifically, the e-tongue detected and differentiated multiple NTs (acetylcholine, dopamine, glycine, glutamate, histamine, and tyrosine) at concentrations as low as 1 nmol L^{-1} and quantified NTs present in a mixture. Besides, analyses performed with interferents and actual samples confirmed the system's potential to be used in clinical diagnostics. The results demonstrate that the MXene-based e-tongue is a suitable, rapid, and simple method for NT monitoring with high accuracy and sensitivity.

1. Introduction

Neurotransmitters (NTs) are essential endogenous molecules secreted by the neurons. They are considered the body's chemical messengers since they are involved in transferring information between neurons and to different parts of the body (Madhurantakam et al., 2020). They are responsible for fundamental brain and body functions, including brain development, memory, emotions, learning, blood pressure, appetite, and sleep (Baranwal and Chandra, 2018; Chauhan et al., 2020b). Due to their crucial role, the NTs are involved in many important processes, while several diseases and neurological disabilities have been attributed to imbalances in NT levels. Therefore, detecting NTs at small concentrations is fundamental for early diagnostics for preventing severe disorders or defining treatments to avoid or reduce risk factors and irreversible complications (Arumugasamy et al., 2020; Madhurantakam et al., 2020).

To better understand the brain's chemical behaviors and act more assertively in the remediation and prevention of neurodegenerative diseases, simultaneous detection and quantification of multiple NTs in a single analysis is an important task to be sought since neurological processes usually involve different NTs (Arumugasamy et al., 2020; Baranwal and Chandra, 2018). For instance, Alzheimer's disease, dementia, and schizophrenia are associated with abnormal levels of both acetylcholine (ACh) and dopamine (DA) (Madhurantakam et al., 2020). A usual method for detecting and quantifying NTs is microdialysis, which consists of injecting a semipermeable probe into the brain. However, this is an invasive procedure that can cause brain damage (Madhurantakam et al., 2020). High-pressure liquid chromatography, capillary electrophoresis, mass spectroscopy, and electroencephalography are other conventional techniques used in NTs detection. However, these methods are typically expensive, time-consuming, and require trained personnel and sophisticated equipment, which limit

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their portability and use in routine tests (Baranwal and Chandra, 2018; He et al., 2023). Due to the drawbacks associated with these conventional analysis techniques, electronic and electrochemical (bio)sensors have been developed as low-cost alternatives for NTs detection (Chauhan et al., 2017; Zhao et al., 2023). These sensors can enable rapid analysis in a wide detection range with high sensitivity using only small sample amounts. However, this detection method is not without challenges, as the simultaneous detection and differentiation of NTs in mixtures and more complex media can result in inconclusive data (He et al., 2023; Madhurantakam et al., 2020). Moreover, these sensors may require the immobilization of bioreceptors for specific NTs detection (Batra and Pundir, 2013; Chauhan et al., 2020a), which can lead to the degradation of the sensor over time and result in a significant loss of performance.

When there is a need for simultaneous detection and quantification of multiple NTs, electronic tongue (e-tongue) sensors emerge as an attractive alternative. An e-tongue is a sensor array that has been successfully utilized for analyzing complex liquid systems (Belugina et al., 2022; Lvova et al., 2016). Its operation is based on the global selective concept, which means that an array of poorly-selective materials is employed to obtain non-specific sensing units capable of responding to different components of the solution analyzed (cross-sensitivity) (Kirsanov et al., 2019; Vlasov et al., 2005). In this way, the distinct electrical responses collected by the array for a particular solution can be regarded as its fingerprint, and the results can be interpreted using proper data treatment methods (Facure et al., 2021; Riul Jr. et al., 2010; Vlasov et al., 1996). Such characteristics make e-tongues versatile, enabling their use in many fields, including food analysis (Belugina et al., 2022; Daikuzono et al., 2019; Garcia-Hernandez et al., 2019), environmental monitoring (Facure et al., 2017; Lvova et al., 2016), and taste evaluation (Guedes et al., 2023; Machado et al., 2018), among others (Christinelli et al., 2021; De Queiroz et al., 2016; Lvova et al., 2018). Although the sensing units do not respond selectively to a target analyte, the e-tongue performance is highly dependent on the choice of materials making up these sensing units. In this regard, the sensing system should be made sensitive to minor electrical changes arising from analyte interactions during measurements by choosing the appropriate units that make up the e-tongue (Facure et al., 2021).

Utilizing nanomaterials as sensing units of e-tongues has resulted in excellent detection performances towards varied analytes (Lu et al., 2022; Mercante et al., 2021; Teodoro et al., 2019). While numerous nanomaterials have already been extensively explored for this task, MXenes, which are 2D carbides and nitrides of transition metals, remain an underexplored candidate material to be used as sensing units for e-tongues. The MXene family encompasses materials with different compositions presenting the general $M_{n+1}X_nT_x$ formula, in which M stands for an early transition metal, X is carbon and/or nitrogen, and T_x represents the surface terminations (Gogotsi, 2023; Gogotsi and Anasori, 2019; VahidMohammadi et al., 2021). MXenes are promising sensing materials due to their high specific surface area, tunable chemical composition, customized electronic properties and robust stability (Hantanasirisakul and Gogotsi, 2018). Despite the scarce investigations demonstrating their use in e-tongues, they have shown good performance in electrochemical sensing (Chen et al., 2022; Lee et al., 2020),

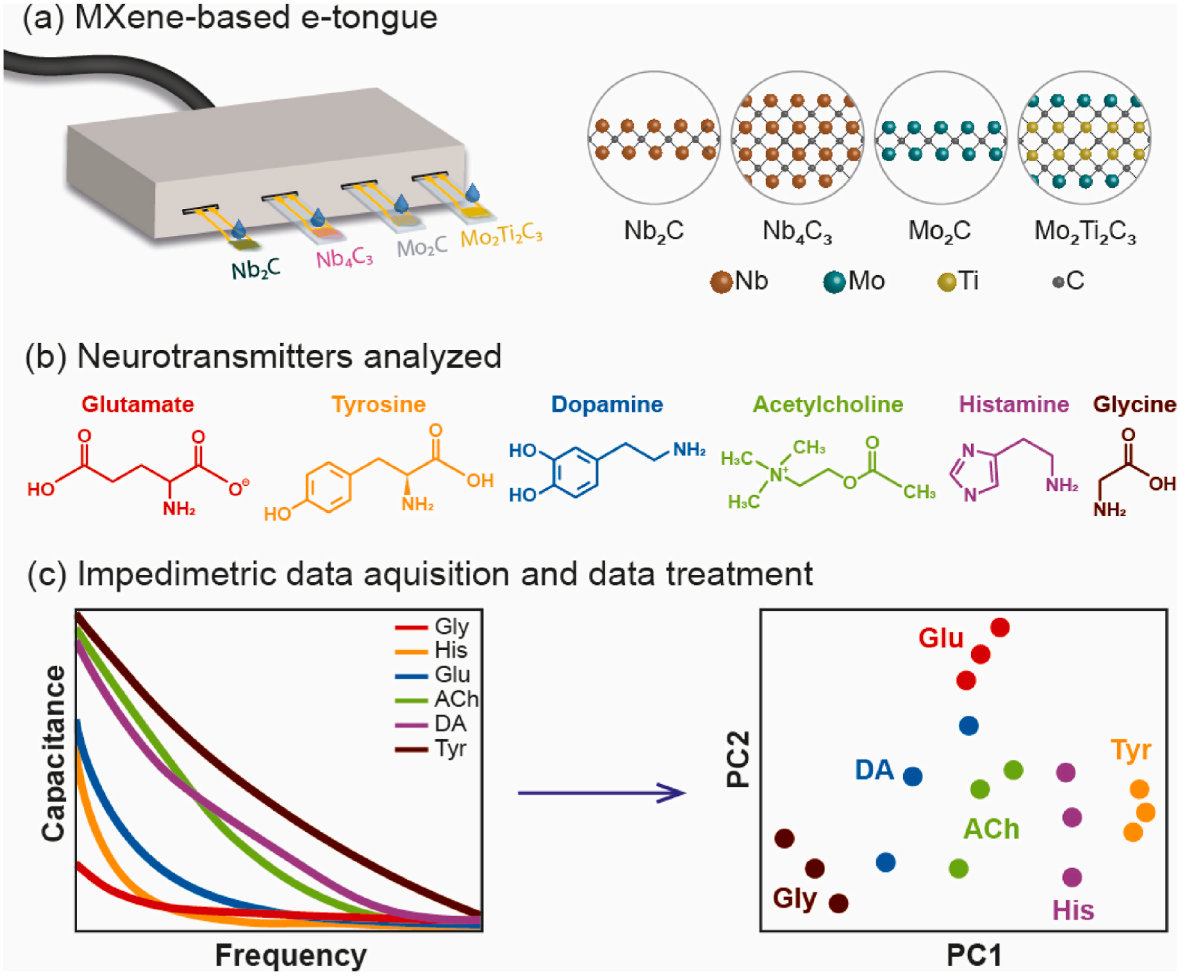

Fig. 1. Schematic illustration of the (a) MXene-based impedimetric e-tongue (surface terminations of MXenes are not shown), (b) the structures of the NTs analyzed, and (c) the representation of the impedimetric analysis performed and the data treatment using the Principal Component Analysis.

gas sensing (Choi et al., 2022), and as constituents of sensor arrays (Li et al., 2022; Sang et al., 2021).

In this work, we report for the first time the use of an all-MXene-based e-tongue for NTs monitoring. As illustrated in Fig. 1a, four sensing units were prepared by modifying gold interdigitated electrodes (IDEs) with Nb_2C, Nb_4C_3, Mo_2C, and $Mo_2Ti_2C_3$. Six NTs were analyzed by the e-tongue (Fig. 1b), and the electrical impedance spectroscopy data were treated with the Principal Component Analysis (PCA) method (Fig. 1c). The e-tongue was able to simultaneously detect multiple NTs and quantify NTs in a mixture, demonstrating the capability of MXenes to be used as highly sensitive sensing materials for e-tongues.

2. Material and methods

2.1. Materials

Powders of titanium (99.5% Thermo Fisher Scientific, −325 mesh), niobium (99.8% Thermo Fisher Scientific, −325 mesh), gallium (99.9% Sigma-Aldrich), molybdenum (99.9% Thermo Fisher Scientific, −250 mesh), aluminum (99.5% Thermo Fisher Scientific, −325 mesh), and graphite (99% Thermo Fisher Scientific, −325 mesh) were used in the synthesis of the MAX phases. Hydrofluoric acid (HF, 51%, Fisher Scientific) and tetramethylammonium hydroxide (TMAH, 25 wt % in water, Sigma-Aldrich) were used in the etching of the MAX phases and the delamination of the synthesized multilayered MXenes, respectively.

Six NTs were analyzed by the e-tongue: dopamine hydrochloride (DA, Sigma-Aldrich), sodium L-glutamate (Glu, ≥99%, Vetec), Glycine (Gly, ≥99%, Sigma-Aldrich), L-tyrosine (Tyr, ≥99%, Sigma-Aldrich), histamine dihydrochloride (His, ≥99%, Sigma-Aldrich), and acetylcholine chloride (ACh, ≥99%, Sigma-Aldrich). L-ascorbic acid (AA, ≥99%, Sigma-Aldrich), D-(+)-glucose (≥99%, Vetec), potassium chloride (KCl, ≥99%, Synth), sodium chloride (NaCl, ≥99%, Synth), and urea (≥99%, Vetec) were used in the interferent analysis.

Monopotassium phosphate (KH_2PO_4) and dibasic potassium phosphate (K_2HPO_4) used in the phosphate buffer solution (PBS) preparation were obtained from Synth.

2.2. MXene syntheses

The syntheses of the Nb_2AlC (Naguib et al., 2013), Nb_4AlC_3 (Zhao et al., 2017), Mo_2Ga_2C (Hu et al., 2015; Lim et al., 2020), and $Mo_2Ti_2AlC_3$ (Saraf et al., 2024) MAX precursors were synthesized as reported previously. To obtain the Nb_2C MXene, 1 g of the MAX phase was added to 10 mL of HF, and the dispersion was stirred for 72 h at room temperature. Nb_4C_3 synthesis was adapted from a method described elsewhere (Zhao et al., 2022). In the procedure, 60 mL of HF was added to 5 g of Nb_4AlC_3 MAX phase. The dispersion was stirred at 50 °C for 7 days. The Mo_2C MXene was obtained by slowly adding 1 g of the MAX phase in 10 mL of HF. The mixture was stirred for 100 h at 55 °C. In the $Mo_2Ti_2C_3$ synthesis, 1 g of the $Mo_2Ti_2AlC_3$ powder was added to 20 mL of HF, and the mixture was stirred at 35 °C for 4 days.

After etching, the multilayered MXenes were washed with repeated centrifugation cycles (3500 rpm for 5 min) to remove the excess of acid. Then, TMAH was used for delaminating the MXenes. For Nb_2C and Mo_2C, 20 mL of a 5 wt% TMAH solution was mixed with the MXene, and the mixture was stirred for 6 h at 35 °C. Nb_4C_3 was delaminated using 10 wt% TMAH by starring the MXene and TMAH mixture at room temperature overnight. The delamination of $Mo_2Ti_2C_3$ was performed by mixing 10 mL of the multilayer MXene with 1 g of TMAH. The mixture was stirred for 2 days at room temperature. After delamination, the mixtures were washed repeatedly with DI water by centrifugation (10000 rpm for 10 min) until the pH was <8. The delaminated MXene dispersions were obtained by re-dispersing the resultant sediment with DI water.

2.3. Physicochemical characterization

UV–vis spectra were collected using a Thermo Scientific (Evolution 201) spectrophotometer, and the samples were placed in quartz cuvettes. Vacuum-filtrated films and a Rigaku SmartLab diffractometer were used to obtain the X-ray diffraction (XRD) patterns of the MXenes. The source was a 40 kV/44 mA X-ray in the 2θ range of 3–65°.

2.4. Neurotransmitter solutions

Three amine NTs (DA, ACh, and His) and three amino acids NTs (Glu, Tyr, and Gly) of medical importance were employed in this work. Stock solutions (1 mmol L^{-1}) were prepared by dissolving the NTs powders in PBS (0.1 mol L^{-1}, pH 7.0). The chemical structures of the NTs are shown in Fig. 1b. The concentrations (1, 10, and 100 nmol L^{-1}) and NTs mixtures were obtained by diluting the stock solutions with PBS. Real samples were prepared using the stock solutions and human urine, diluted 20 times with PBS, and filtrated with a 0.22 μm syringe filter before use. Contaminants' solutions were prepared by diluting glucose, AA, KCl, NaCl, and urea in PBS at 10 nmol L^{-1}.

2.5. Interdigitated electrode modification

Gold IDEs (Fig. S1) were modified with the MXene solutions to obtain the sensing units of the e-tongue. The IDEs were fabricated at the microfabrication laboratory (LMF/LNNano-LNLS, Campinas-Brazil) using photolithography, and glass was used as a substrate. Each IDE comprises 50 pairs of fingers with a width between them of 10 μm. The IDEs were modified by drop-casting 10 μL of a 0.5 mg mL^{-1} MXene (Nb_2C, Nb_4C_3, Mo_2C, and $Mo_2Ti_2C_3$) solution. The IDEs were left to dry overnight at room temperature. The same set of electrodes was used to perform all measurements.

2.6. Impedance spectroscopy measurements

The impedance measurements were performed in a Solartron impedance analyzer (1260 A) and controlled by ZPlot software. Data were collected in triplicate, applying an AC voltage of 250 mV and sweeping the frequency from 10 Hz to 1 MHz (5 pts/dec). Measurements were performed using 10 μL of the NT solution, left in contact with the electrode for 10 min before data acquisition to ensure stability.

2.7. Data treatment

The capacitance data were treated using the PCA method, in which the data dimensionality is reduced, preserving the maximum amount of information (Facure et al., 2020; Ringner, 2008). This method allows for the visualization of multidimensional data sets by plotting the two directions along which there is the largest variation of the data (principal components, PC). Similarities and differences between the samples can be evaluated by their proximity in the PCA plot (Ringner, 2008).

3. Results and discussion

3.1. Materials characterization

The synthesis and delamination of the MXenes were evaluated through XRD and UV–vis measurements. All the XRD patterns (Fig. 2a) show a higher intensity of the (002) peak, while higher ordered peaks, characteristic of MAX phases, are missing or present very low intensity. The predominance of the peak (002) confirms the successful etching of the MAX phases to obtain the MXenes (Fredrickson et al., 2016; Mashtalir et al., 2015; Saraf et al., 2024; Zhao et al., 2017). The (002) peaks are centered at $2\theta = 6.9°$, 3.9°, 7.0°, and 4.9° for Nb_2C, Nb_4C_3, Mo_2C, and $Mo_2Ti_2C_3$, respectively. UV–vis spectra (Fig. 2b) were also used to characterize the materials. The Nb_2C and Mo_2C spectra present

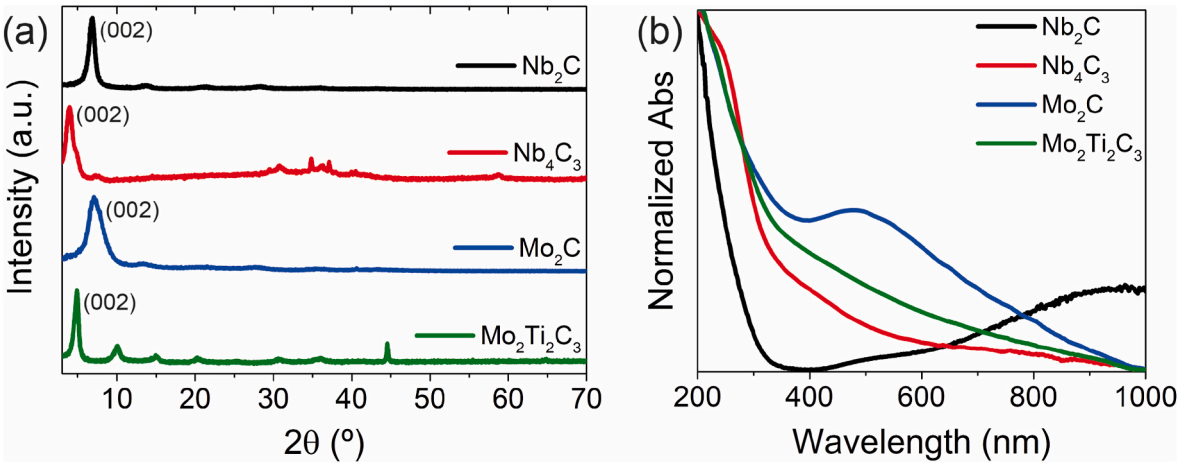

Fig. 2. (a) XRD patterns and (b) UV–vis spectra of Nb_2C, Nb_4C_3, Mo_2C and $Mo_2Ti_2C_3$ MXenes.

absorption peaks with maximum intensity at 965 nm and 480 nm, respectively, whereas the MXenes with three carbon layers (Nb_4C_3 and $Mo_2Ti_2C_3$) did not show any significant excitation peak. The UV–vis spectra obtained are in accordance with those reported in the literature for these materials (Maleski et al., 2021), confirming the success of the MXenes synthesis.

3.2. Electrical characterization and neurotransmitters detection

The modified electrodes were characterized using electrical impedance spectroscopy. Fig. 3 shows the capacitance curves obtained in PBS in the frequency range from 10 Hz to 1 MHz. The MXene films used in the IDEs modification led to different capacitance values, confirming the successful functionalization of the IDEs. Interestingly, the electrodes functionalized with Nb-based MXenes presented a near-constant decrease in the capacitance over the entire frequency range, while those containing Mo showed a greater reduction of capacitance values in the frequency range from 10 to 100 Hz.

The electrodes were then used in the analyses of the NT solutions. Fig. S2 shows the change in capacitance over the frequencies from 10 Hz to 1 MHz for each NT tested. Moreover, the measured capacitance values show that each MXene responds to the NTs in a particular way. These different behaviors demonstrate the cross-sensitivity of the e-tongue, i.e., the array is composed of non-specific sensing units that can respond distinctly to the liquid under analysis, contributing to reaching the global selectivity typical of e-tongues (Facure et al., 2023; Vlasov et al., 2005).

The capacitance responses of the e-tongue obtained in the analyses of the NT solutions in PBS were treated by the PCA method. The PBS was used to guarantee stable conditions (constant pH) during measurements, in a way that any electrical variation could be related only to the analytes. The PCA plot (Fig. 4) shows that the e-tongue was able to detect and differentiate each NT analyzed, presenting no superposition between distinct analytes. The PBS samples are localized separately in the region of negative PC1 and positive PC2 values, which indicates the ability of the e-tongue to identify the presence of NTs in the solution, while also confirming the reliability of the MXene e-tongue to detect multiple NTs. Moreover, the system could discriminate the solutions with respect to their concentrations. The proximity between the points of the same sample reflects the robust reproducibility observed throughout the experiments. It is important to highlight that the e-tongue was able to simultaneously detect different NTs, which is fundamental for understanding disease mechanisms and achieving a

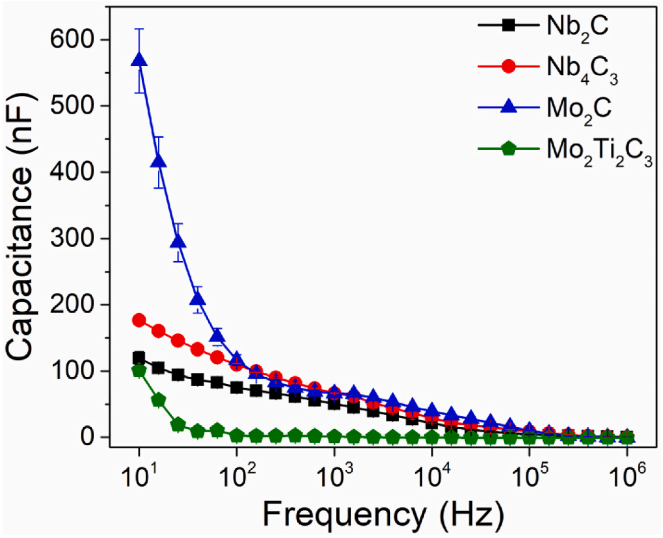

Fig. 3. Capacitance data collected in PBS with the MXene-modified IDEs in the frequency range from 10 Hz to 1 MHz.

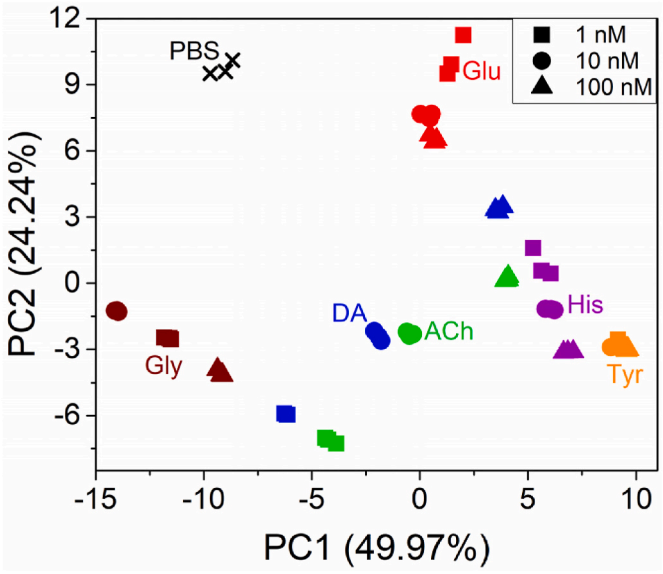

Fig. 4. PCA plot obtained by treating the capacitance data collected at 250 mV from 10 Hz to 1 MHz with the e-tongue for the NTs solutions (DA: dopamine, Glu: glutamate, Gly: glycine, ACh: acetylcholine, His: histamine, and Tyr: tyrosine) at different concentrations (1, 10, and 100 nmol L^{-1}) and pure PBS.

precise medical diagnosis (Baranwal and Chandra, 2018; Madhurantakam et al., 2020).

3.3. Neurotransmitters' mixtures analyses

Given the ability of the e-tongue to simultaneously detect isolated NTs, the system was then tested for NT detection in mixtures, which is a more realistic condition found in clinical samples (Madhurantakam et al., 2020). To simulate this, NTs from different classes were used to prepare the mixtures. The PCA plot in Fig. 5a shows four different regions related to the PC1 value. Only the PBS sample is in the first region, with PC1 values less than −10. The samples containing only one NT are located in the region with PC1 values ranging from −10 to 0. All the NT mixtures are located on the positive PC1 side of the PCA graph in Fig. 5a, which indicates the ability of the e-tongue to detect NT mixtures. The samples containing two NTs are located in the region of PC1 values between 0 and 8, while the mixture containing three NTs is situated in the region with PC1 values higher than 8. Since all NT solutions were prepared at the same concentration (10 nmol L^{-1}), the data show that the e-tongue was able to differentiate the NT solutions according to the number of NTs present in the mixture.

The analysis of NTs concentration in a mixture was also performed. When the concentration of ACh was fixed at 2.5 nmol L^{-1} and the concentration of His varied from 1 to 7.5 nmol L^{-1}, the e-tongue was able to differentiate each mixture, as displayed in the PCA plot of Fig. 5b. Moreover, with the increase in the His concentration, the PC1 value decreases. Fig. 5c shows a linear relationship between the average PC1 value and the logarithm of His concentration. These results demonstrate that the MXene-based e-tongue represents an exciting alternative for analyzing NTs in mixtures, as it is able to detect the presence of multiple NTs and estimate their concentration in solutions.

3.4. Real sample analyses

To evaluate the applicability of the MXene e-tongue in real conditions, analyses of human urine contaminated with NTs and possibly interfering substances were performed. Contaminated solutions were prepared in concentrations of 1 nmol L^{-1} and 100 nmol L^{-1}, and the obtained PCA plots are shown in Fig. 6a and b, respectively. In both PCA plots, the interferents are isolated on the negative PC1 values side, while the contaminated solutions are located on positive PC1 values. As observed when the analyses were carried out in PBS, the e-tongue could differentiate each NT and distinguish the contaminated samples from the non-contaminated ones. This confirms the ability of the system to detect NTs in more complex media/real environments and shows that other analytes that may be present in urine samples did not affect the performance of the e-tongue.

4. Conclusions

An all-MXene e-tongue was fabricated using gold IDEs modified with Nb_2C, Nb_4C_3, Mo_2C, and $Mo_2Ti_2C_3$ to detect neurotransmitters (NTs), namely acetylcholine, dopamine, glycine, glutamate, histamine, and tyrosine. The high specific surface area and chemical stability of the MXenes allied to their distinct electrical properties led to a system with good reproducibility and high sensitivity towards NT detection. The MXene-based e-tongue showed the capacity to simultaneously detect and distinguish NTs at low concentrations without the use of specific (bio)recognition elements. When analyzing NT mixtures, the system could differentiate the mixtures by the number of NTs present in the solution, and a correlation between the concentration of an NT and the PC1 value of the PCA graph was observed. The analyses were also performed with contaminated urine, showing that the e-tongue was able to differentiate the NTs in more complex and real matrix, in which the presence of potential contaminants did not impair the e-tongue performance. The results demonstrate the potential of the developed sensor to

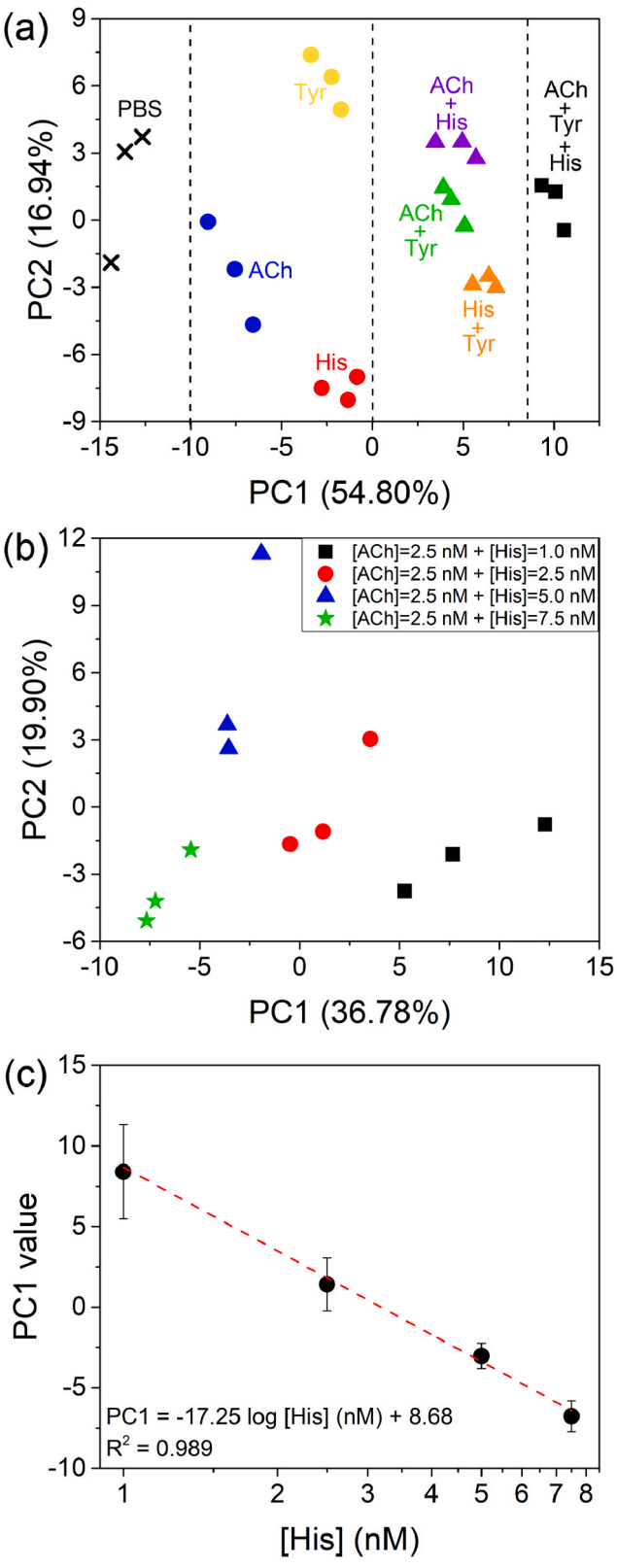

Fig. 5. PCA plots obtained by treating the capacitance data collected at 250 mV from 10 Hz to 1 MHz with the e-tongue for (a) PBS and the NTs solutions (ACh: acetylcholine, His: histamine, Tyr: tyrosine, ACh + His, ACh + Tyr, His + Tyr, and ACh + His + Tyr) at 10 nmol L^{-1} and for (b) mixtures containing a fixed concentration of ACh (2.5 nmol L^{-1}) and varied concentrations of His (1.0, 2.5, 5.0, and 7.0 nmol L^{-1}). (c) Average PC1 value versus the logarithm concentration of His in the mixture containing 2.5 nmol L^{-1} of ACh.

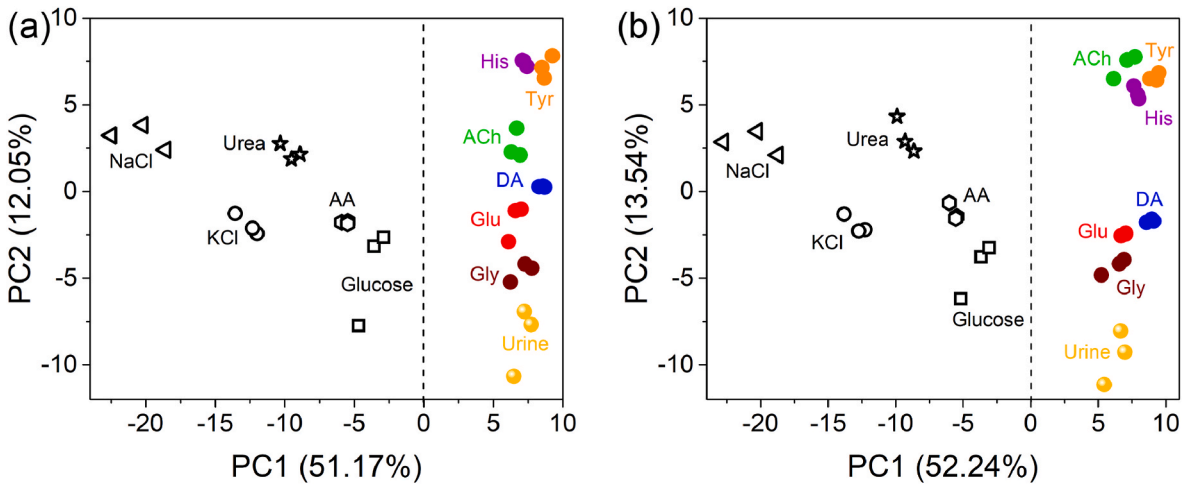

Fig. 6. PCA plots obtained treating the capacitance data collected at 250 mV from 10 Hz to 1 MHz with the e-tongue for the NTs solutions (DA: dopamine, Glu: glutamate, Gly: glycine, ACh: acetylcholine, His: histamine, and Tyr: tyrosine) prepared with human urine (real samples) at (a) 1 nmol L^{-1} and (b) 100 nmol L^{-1} and interferents (10 nmol L^{-1}).

be used for NT monitoring in clinical samples. Furthermore, employing MXenes as sensing units in an e-tongue demonstrated their diverse capabilities beyond the extensively studied Ti_3C_2 structure. Finally, the system enables the fabrication of reliable and portable devices for on-site and real-time NT analysis, paving the way for exploring MXenes in other sensor arrays.

CRediT authorship contribution statement

Murilo H.M. Facure: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gulnaz Gahramanova:** Writing – review & editing, Methodology. **Danzhen Zhang:** Writing – review & editing, Methodology. **Teng Zhang:** Writing – review & editing, Methodology. **Christopher E. Shuck:** Writing – review & editing, Methodology. **Luiza A. Mercante:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Daniel S. Correa:** Writing – review & editing, Supervision, Resources, Conceptualization. **Yury Gogotsi:** Writing – review & editing, Supervision, Resources.

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.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2024.116526.

References

Arumugasamy, S.K., Chellasamy, G., Gopi, S., Govindaraju, S., Yun, K., 2020. Current advances in the detection of neurotransmitters by nanomaterials: an update. TrAC, Trends Anal. Chem. 123, 115766 https://doi.org/10.1016/j.trac.2019.115766.

Baranwal, A., Chandra, P., 2018. Clinical implications and electrochemical biosensing of monoamine neurotransmitters in body fluids, in vitro, in vivo, and ex vivo models. Biosens. Bioelectron. 121, 137–152. https://doi.org/10.1016/j.bios.2018.09.002.

Batra, B., Pundir, C.S., 2013. An amperometric glutamate biosensor based on immobilization of glutamate oxidase onto carboxylated multiwalled carbon nanotubes/gold nanoparticles/chitosan composite film modified Au electrode. Biosens. Bioelectron. 47, 496–501. https://doi.org/10.1016/j.bios.2013.03.063.

Belugina, R., Senchikhina, A., Volkov, S., Fedorov, A., Legin, A., Kirsanov, D., 2022. Quantification of phosphatides in sunflower oils using a potentiometric e-tongue. Anal. Methods 14, 3064–3070. https://doi.org/10.1039/D2AY00736C.

Chauhan, N., Chawla, S., Pundir, C.S., Jain, U., 2020a. Sensitive biosensing of neurotransmitter: 2D material wrapped nanotubes and MnO_2 composites for the detection of acetylcholine. Synth. Met. 263, 116354 https://doi.org/10.1016/j.synthmet.2020.116354.

Chauhan, N., Chawla, S., Pundir, C.S., Jain, U., 2017. An electrochemical sensor for detection of neurotransmitter-acetylcholine using metal nanoparticles, 2D material and conducting polymer modified electrode. Biosens. Bioelectron. 89, 377–383. https://doi.org/10.1016/j.bios.2016.06.047.

Chauhan, N., Soni, S., Agrawal, P., Balhara, Y.P.S., Jain, U., 2020b. Recent advancement in nanosensors for neurotransmitters detection: present and future perspective. Process Biochemistry 91, 241–259. https://doi.org/10.1016/j.procbio.2019.12.016.

Chen, L., Chen, F., Liu, G., Lin, H., Bao, Y., Han, D., Wang, W., Ma, Y., Zhang, B., Niu, L., 2022. Superhydrophobic functionalized $Ti_3C_2T_x$ MXene-based skin-attachable and wearable electrochemical pH sensor for real-time sweat detection. Anal. Chem. 94, 7319–7328. https://doi.org/10.1021/acs.analchem.2c00684.

Choi, J., Chacon, B., Park, H., Hantanasirisakul, K., Kim, T., Shevchuk, K., Lee, J., Kang, H., Cho, S.-Y., Kim, J., Gogotsi, Y., Kim, S.J., Jung, H.-T., 2022. N–p-Conductor transition of gas sensing behaviors in Mo_2CT_x MXene. ACS Sens. 7, 2225–2234. https://doi.org/10.1021/acssensors.2c00658.

Christinelli, W.A., Shimizu, F.M., Facure, M.H.M., Cerri, R., Oliveira, Jr.O.N., Correa, D. S., Mattoso, L.H.C., 2021. Two-dimensional MoS_2-based impedimetric electronic tongue for the discrimination of endocrine disrupting chemicals using machine learning. Sens Actuators B Chem 336, 129696. https://doi.org/10.1016/j.snb.2021.129696.

Daikuzono, C.M., Delaney, C., Morrin, A., Diamond, D., Florea, L., Oliveira, O.N., 2019. Paper based electronic tongue - a low-cost solution for the distinction of sugar type and apple juice brand. Analyst 144, 2827–2832. https://doi.org/10.1039/c8an01934g.

De Queiroz, D.P., Florentino, A.D.O., Bruno, J.C., Da Silva, J.H.D., Riul, A., Giacometti, J. A., 2016. The use of an e-tongue for discriminating ethanol/water mixtures and determination of their water content. Sens Actuators B Chem 230, 566–570. https://doi.org/10.1016/j.snb.2016.02.080.

Facure, M.H.M., Andre, R.S., Mercante, L.A., Fugikawa-Santos, L., Oliveira, O.N., Correa, D.S., 2021. Fundamentals and applications of impedimetric electronic tongues. In: Electronic Tongues. IOP Publishing, pp. 6–32. https://doi.org/10.1088/978-0-7503-3687-1ch6.

Facure, M.H.M., Braunger, M.L., Mercante, L.A., Paterno, L.G., Riul, A., Correa, D.S., 2023. Electrical impedance-based electronic tongues. In: Encyclopedia of Sensors and Biosensors. Elsevier, Oxford, pp. 567–590. https://doi.org/10.1016/B978-0-12-822548-6.00091-1.

Facure, M.H.M., Mercante, L.A., Mattoso, L.H.C., Correa, D.S., 2017. Detection of trace levels of organophosphate pesticides using an electronic tongue based on graphene

hybrid nanocomposites. Talanta 167, 59–66. https://doi.org/10.1016/j.talanta.2017.02.005.
Facure, M.H.M., Schneider, R., dos Santos, D.M., Correa, D.S., 2020. Impedimetric electronic tongue based on molybdenum disulfide and graphene oxide for monitoring antibiotics in liquid media. Talanta 217, 121039. https://doi.org/10.1016/j.talanta.2020.121039.
Fredrickson, K.D., Anasori, B., Seh, Z.W., Gogotsi, Y., Vojvodic, A., 2016. Effects of applied potential and water intercalation on the surface chemistry of Ti_2C and Mo_2C MXenes. J. Phys. Chem. C 120, 28432–28440. https://doi.org/10.1021/acs.jpcc.6b09109.
Garcia-Hernandez, C., Garcia-Cabezon, C., Martin-Pedrosa, F., Rodriguez-Mendez, M.L., 2019. Analysis of musts and wines by means of a bio-electronic tongue based on tyrosinase and glucose oxidase using polypyrrole/gold nanoparticles as the electron mediator. Food Chem. 289, 751–756. https://doi.org/10.1016/j.foodchem.2019.03.107.
Gogotsi, Y., 2023. MXenes: from Discovery to Applications of Two-Dimensional Metal Carbides and Nitrides, first ed. Jenny Stanford Publishing.
Gogotsi, Y., Anasori, B., 2019. The rise of MXenes. ACS Nano 13, 8491–8494. https://doi.org/10.1021/acsnano.9b06394.
Guedes, M.D.V., Marques, M.S., Berlitz, S.J., Facure, M.H.M., Correa, D.S., Steffens, C., Contri, R.V., Külkamp-Guerreiro, I.C., 2023. Lamivudine and zidovudine-loaded nanostructures: green chemistry preparation for pediatric oral administration. Nanomaterials 13, 770. https://doi.org/10.3390/nano13040770.
Hantanasirisakul, K., Gogotsi, Y., 2018. Electronic and optical properties of 2D transition metal carbides and nitrides (MXenes). Adv. Mater. 30, 1804779 https://doi.org/10.1002/adma.201804779.
He, J., Spanolios, E., Froehlich, C.E., Wouters, C.L., Haynes, C.L., 2023. Recent advances in the development and characterization of electrochemical and electrical biosensors for small molecule neurotransmitters. ACS Sens. 8, 1391–1403. https://doi.org/10.1021/acssensors.3c00082.
Hu, C., Lai, C.-C., Tao, Q., Lu, J., Halim, J., Sun, L., Zhang, J., Yang, J., Anasori, B., Wang, J., Sakka, Y., Hultman, L., Eklund, P., Rosen, J., Barsoum, M.W., 2015. Mo_2Ga_2C: a new ternary nanolaminated carbide. Chem. Commun. 51, 6560–6563. https://doi.org/10.1039/C5CC00980D.
Kirsanov, D., Correa, D.S., Gaal, G., Riul, A., Braunger, M.L., Shimizu, F.M., Oliveira, O. N., Liang, T., Wan, H., Wang, P., Oleneva, E., Legin, A., 2019. Electronic tongues for inedible media. Sensors 19, 1–20. https://doi.org/10.3390/s19235113.
Lee, S.H., Eom, W., Shin, H., Ambade, R.B., Bang, J.H., Kim, H.W., Han, T.H., 2020. Room-temperature, highly durable $Ti_3C_2T_x$ MXene/graphene hybrid fibers for NH_3 gas sensing. ACS Appl. Mater. Interfaces 12, 10434–10442. https://doi.org/10.1021/acsami.9b21765.
Li, B., Zhu, Q.-B., Cui, C., Liu, C., Wang, Z.-H., Feng, S., Sun, Y., Zhu, H.-L., Su, X., Zhao, Y.-M., Zhang, H.-W., Yao, J., Qiu, S., Li, Q.-W., Wang, X.-M., Wang, X.-H., Cheng, H.-M., Sun, D.-M., 2022. Patterning of wafer-scale MXene films for high-performance image sensor arrays. Adv. Mater. 34, 2201298 https://doi.org/10.1002/adma.202201298.
Lim, K.R.G., Handoko, A.D., Johnson, L.R., Meng, X., Lin, M., Subramanian, G.S., Anasori, B., Gogotsi, Y., Vojvodic, A., Seh, Z.W., 2020. 2H-MoS_2 on Mo_2CT_x MXene nanohybrid for efficient and durable electrocatalytic hydrogen evolution. ACS Nano 14, 16140–16155. https://doi.org/10.1021/acsnano.0c08671.
Lu, L., Hu, Z., Hu, X., Li, D., Tian, S., 2022. Electronic tongue and electronic nose for food quality and safety. Food Res. Int. 162, 112214 https://doi.org/10.1016/j.foodres.2022.112214.
Lvova, L., Guanais Gonçalves, C., Petropoulos, K., Micheli, L., Volpe, G., Kirsanov, D., Legin, A., Viaggiu, E., Congestri, R., Guzzella, L., Pozzoni, F., Palleschi, G., Di Natale, C., Paolesse, R., 2016. Electronic tongue for microcystin screening in waters. Biosens. Bioelectron. 80, 154–160. https://doi.org/10.1016/j.bios.2016.01.050.
Lvova, L., Yaroshenko, I., Kirsanov, D., Di Natale, C., Paolesse, R., Legin, A., 2018. Electronic tongue for brand uniformity control: a case study of apulian red wines recognition and defects evaluation. Sensors 18. https://doi.org/10.3390/s18082584.
Machado, J.C., Shimizu, F.M., Ortiz, M., Pinhatti, M.S., Carr, O., Guterres, S.S., Oliveira, O.N., Volpato, N.M., 2018. Efficient praziquantel encapsulation into polymer microcapsules and taste masking evaluation using an electronic tongue. Bull. Chem. Soc. Jpn. 91, 865–874. https://doi.org/10.1246/bcsj.20180005.
Madhurantakam, S., Karnam, J.B., Brabazon, D., Takai, M., Ahad, I.U., Balaguru Rayappan, J.B., Krishnan, U.M., 2020. "Nano": an emerging avenue in electrochemical detection of neurotransmitters. ACS Chem. Neurosci. 11, 4024–4047. https://doi.org/10.1021/acschemneuro.0c00355.
Maleski, K., Shuck, C.E., Fafarman, A.T., Gogotsi, Y., 2021. The broad chromatic range of two-dimensional transition metal carbides. Adv. Opt. Mater. 9, 2001563 https://doi.org/10.1002/adom.202001563.
Mashtalir, O., Lukatskaya, M.R., Zhao, M.-Q., Barsoum, M.W., Gogotsi, Y., 2015. Amine-assisted delamination of Nb_2C MXene for Li-ion energy storage devices. Adv. Mater. 27, 3501–3506. https://doi.org/10.1002/adma.201500604.
Mercante, L.A., Andre, R.S., Facure, M.H.M., Fugikawa-Santos, L., Correa, D.S., 2021. Design of a bioelectronic tongue for glucose monitoring using zinc oxide nanofibers and graphene derivatives. Sensors and Actuators Reports 3, 100050. https://doi.org/10.1016/j.snr.2021.100050.
Naguib, M., Halim, J., Lu, J., Cook, K.M., Hultman, L., Gogotsi, Y., Barsoum, M.W., 2013. New two-dimensional niobium and vanadium carbides as promising materials for Li-ion batteries. J. Am. Chem. Soc. 135, 15966–15969. https://doi.org/10.1021/ja405735d.
Ringner, M., 2008. What is principal component analysis? Nat. Biotechnol. 26, 303–304. https://doi.org/10.1038/nbt0308-303.
Riul, Jr.A., Dantas, C.A.R., Miyazaki, C.M., Oliveira, Jr.O.N., 2010. Recent advances in electronic tongues. Analyst 135, 2481–2495. https://doi.org/10.1039/C0AN00292E.
Sang, S., Jing, Z., Cheng, Y., Ji, C., Zhang, Q., Dong, X., 2021. Graphene and MXene-based sponge pressure sensor array for rectal model pressure detection. Macromol. Mater. Eng. 306, 2100251 https://doi.org/10.1002/mame.202100251.
Saraf, M., Chacon, B., Ippolito, S., Lord, R.W., Anayee, M., Wang, R., Inman, A., Shuck, C. E., Gogotsi, Y., 2024. Enhancing charge storage of $Mo_2Ti_2C_3$ MXene by partial oxidation. Adv. Funct. Mater. 34, 2306815 https://doi.org/10.1002/adfm.202306815.
Teodoro, K.B.R., Shimizu, F.M., Scagion, V.P., Correa, D.S., 2019. Ternary nanocomposites based on cellulose nanowhiskers, silver nanoparticles and electrospun nanofibers: use in an electronic tongue for heavy metal detection. Sens Actuators B Chem 290, 387–395. https://doi.org/10.1016/j.snb.2019.03.125.
VahidMohammadi, A., Rosen, J., Gogotsi, Y., 2021. The world of two-dimensional carbides and nitrides (MXenes). Science 372, eabf1581. https://doi.org/10.1126/science.abf1581.
Vlasov, Yu, Legin, A., Rudnitskaya, A., Di Natale, C., D'Amico, A., 2005. Nonspecific sensor arrays ("electronic tongue") for chemical analysis of liquids. Pure Appl. Chem. 77, 1965–1983. https://doi.org/10.1351/pac200577111965.
Vlasov, Y.G., Legin, A.V., Rudnitskaya, A.M., Di Natale, C., D'Amico, A., 1996. Multisensor system with an array of chemical sensors and artificial neural networks (electronic tongue) for quantitative analysis of multicomponent aqueous solutions. Russ. J. Appl. Chem. 69, 848–853.
Zhao, C., Cheung, K.M., Huang, I.-W., Yang, H., Nakatsuka, N., Liu, W., Cao, Y., Man, T., Weiss, P.S., Monbouquette, H.G., Andrews, A.M., 2023. Implantable aptamer–field-effect transistor neuroprobes for in vivo neurotransmitter monitoring. Sci. Adv. 7, eabj7422 https://doi.org/10.1126/sciadv.abj7422.
Zhao, S., Meng, X., Zhu, K., Du, F., Chen, G., Wei, Y., Gogotsi, Y., Gao, Y., 2017. Li-ion uptake and increase in interlayer spacing of Nb_4C_3 MXene. Energy Storage Mater. 8, 42–48. https://doi.org/10.1016/j.ensm.2017.03.012.
Zhao, S., Wang, X., Kurra, N., Gogotsi, Y., Gao, Y., 2022. Effect of pinholes in Nb_4C_3 MXene sheets on its electrochemical behavior in aqueous electrolytes. Electrochem. Commun. 142, 107380 https://doi.org/10.1016/j.elecom.2022.107380.