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Gas Sensor Based on Biohydroxyapatite to Study the Volatile Compounds of Nasal Secretion

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Abstract: The paper investigates the properties of gas sensors based on biohydroxyapatite for diagnostic the state of the upper respiratory tract of calves and humans. The process of synthesis of biohydroxyapatite of different mass is described. The peculiarities of sorption of volatile compounds on this sorbent depending on mass are considered for two modes of measurement (injection and frontal). The effectiveness and selectiveness of organic vapor microweighting using biohydroxyapatite phases of different mass are estimated. Possibilities of volatile organic compounds vapors identification in a mixture without separation are considered. For this task, the new parameters are calculated by the signals of one or two piezoelectric sensors with biohydroxyapatite of different masses. Results of analysis and identification of substances in the gas phase over nasal secretions of calves and humans with various respiratory diseases are presented. The intervals of the values of the calculated parameters are determined for reliable selection of samples into the "inflammation" group. The first and second order errors have been estimated in binary classification into groups "healthy" and "inflammation". The minimum number of false-positive responses in the classification of samples is achieved using the parameters of two sensors with a biohydroxyapatite of different masses.

Keywords: Sensors, Biohydroxyapatite, Sorption, Volatile organic compounds, Diagnostics, Upper respiratory tract, Inflammation, Nasal secretion.

1. Introduction

When analyzing biological samples, it is essential to minimize the number of analysis stages and the changes in the native state of the samples by preparation for measurement (heating, sorption, extraction, freezing). The use of an array of sensitive gas sensors ("electronic nose" or E-nose) simplifies preparation stages as much as possible and allows to fix the integral profile of the most informative part of the metabolome - volatile compounds. This approach has been widely used to analyze various human and animal samples over the past ten years [1].

The most popular biosamples for analysis are exhaled air, blood, urine, sweat, saliva and others [2-5]. Also, it was established that the nasal secretion of calves is an informative biosample as the exhaled breath condensate when diagnostic of respiratory

diseases by detecting volatile compounds using arrays of piezoelectric sensors [6-8]. The results are relevant and valuable for developing portable devices for on-farm diagnosis [9].

We believe that the approach is universal and can be extended to human biosamples. It is vital for monitoring the inflammation of the lungs and larynx in humans when infected with viruses, including SARS-CoV-2 and E-nose technologies are perspectives for that [10].

Using the new materials for sensitive coatings of measurement elements in E-nose increases the stability, sensitivity, operating time and expands the possibilities of sensors application in various conditions [11-12].

Earlier, the parameters of sorption of volatile compounds using the phase of biohydroxyapatite were implemented to analyze the results of sorption of the gas phase of nasal secretion samples [13].

This work aims to investigate the features of sorption of volatile compounds by biohydroxyapatite phases of different masses and apply the sensors based on it to estimate the presence of upper respiratory tract inflammation by analysis of gas phases over human and animal nasal secretions.

2. Materials and Objects

The study was carried out on the device "MCNanoW-PQ" (LLC "Sensorika – New Technologies", Voronezh, Russia) with eight working channels [14]. The multichannel device is connected with a laptop via the MCW-Soft for registering changes in the biohydroxyapatite phase mass in real-time with a step of 1 s and a sensitivity of 1 ng. Multichannel nanobalances are equipped with a sealed fluoroplastic cell with a volume of 60.0 cm^3 with a cap and nozzles for introducing vapors, both individual compounds and their mixtures in different modes – frontal, injection. Piezoelectric quartz resonators (PQR) with a base frequency of 10.0 and 14.0 MHz were used to manufacture sensors.

The phase of hydroxyapatite (HA) was studied as a sorbent. Hydroxyapatite $Ca_5(PO_4)_3OH$ was obtained by the sol-gel technique developed at the University named after N. I. Lobachevsky [15]. Reagent concentrations were optimized to obtain nanoparticles with good sorption properties [16].

The hydroxyapatite phase from acetone (0.5 g of phase/10 ml) was uniformly deposited to the electrodes of the piezoelectric quartz resonator, defatted with acetone, by immersion in an ultrasonic suspension [17]. The mass of the phases from 1 to 7 μg was obtained by varying the exposure time of the resonator in the suspension (from 5 to 15 s) to control the sensitivity and selectivity of microweighing of substances vapors. The free solvent was removed in an oven (40 minutes at t from 50 °C), placing the PQR in the holder vertically. Hydroxyapatite synthesized by the sol-gel method is a nanostructured material compatible with biological tissues; therefore, we assumed its unique sorption properties to volatile biomolecules that are excreted during the life of organisms. The microstructure of HA coatings was investigated on a Solver P447-PRO (CJSC "NT-MDT", Russia) atomic force microscope (AFM) with a video surveillance system to substantiate and explain the dependence of the sorption properties of HA of different mass.

Vapors of individual volatile organic compounds were selected as sorbats (LLC "Reakhim", Russia): (VOCs): aliphatic alcohols C_2–C_5, normal and isomeric structure; ketones (acetone, methyl ethyl ketone), arenas (benzene, toluene, phenol), amines (methylamine, diethylamine), aliphatic acids C_2, C_4, C_5; chloroform, C_2-C_5 alkyl acetates, acetaldehyde. We also investigated the sorption of water vapor (bidistillate, with electrical conductivity control) as the main component of biosample, which can interfere with the detection of analytes.

The vibration frequency of the quartz plate changes during sorption of substances on the HA phases, deposited on the PQR electrodes. According to the Sauerbrey model, the change in the vibration frequency of the piezoelectric sensor ($-\Delta F_{max}$, Hz) is proportional to the mass of the sorbate Δm (μg) on its electrodes at any moment of sorption time. This model was also used to calculate the mass of the sorbent phases on the piezoelectric balance electrodes (m_{HA}, μg) as mentioned in [16].

The mass of individual volatile compounds during sorption is measured at a temperature of (20.0 ± 0.5 °C) using two modes of vapor input (Fig. 1). In the injection mode, a 5.0 cm^3 sample of an individual substance was placed in a glass sealed vessel, which was closed with a soft polymer membrane and kept for 20-30 min at a temperature of (20 ± 1) ºC until equilibrium was established in the "liquid – vapor" system. After that, a certain volume of the equilibrium gas phase (EGP) over the substance was taken by an individual syringe and introduced into the detection cell of the device at a rate of 1 cm^3/s. The mass concentration of vapors of substances in the detection cell was varied by changing the volume of the EGP from 0.5 to 5.0 cm^3 with a step of 0.5 cm^3.

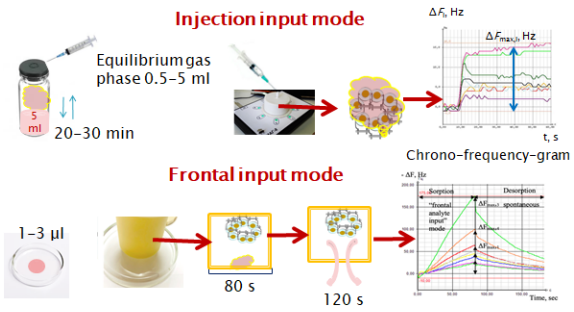

Fig. 1. The scheme of sorbtion measurement.

The VOC vapor sorption for each concentration was measured 5-7 times. After checking the system's stability and starting the measurement, the vapors

were introduced into the near-sensor space. The frontal mode of vapor input into the detection cell was carried out under static conditions (without a carrier gas) due to spontaneous diffusion of vapors into the near-sensor space from the source (sample of an individual compound) in a closed nozzle body. The particular volume of substances (from 1 to 3 μl for each substance) was placed onto the glass Petri plate and covered by the detection cell of the device with sensors for 80 seconds. Substances were evaporated entirely during that time, the response of sensors were recorded in the 80 s. After that, the detection cell was opened for the spontaneous desorption of gases from sensor coverings. The mass concentrations, frontal input mode of measurement are more completely described in work [8].

To calculate the sorption parameters $A(i/j)$ [18], we used a quantitative signal of piezoelectric balances with a sorbent — the maximum change in the oscillation frequency of the piezoelectric sensor ($-\Delta F_{max}$, Hz), which characterizes the efficiency of sorption of compounds on the sorbent phases.

Samples of nasal secretion from calves (n=50) and humans (n=17) were selected using sterile cotton swabs. Samples of calf's nasal secretion were simultaneously investigated by bacteriological and molecular-genetic methods. The animals were auscultated and clinically examined by specialists according to Wisconsin respiratory scoring chart [19]. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethic Committee of Voronezh State University of Engineering Technologies (protocol № 2 dated 25 February 2021). The clinical examination of the volunteers by the specialist established the presence or absence of inflammation in humans.

The group of "inflammation" consisted of samples from animals with bovine respiratory disease (n=10) (diagnosis based on results of clinical and laboratory examination) and from a human with the first sign of respiratory disease according to anamnesis and clinical examination (n=10). The "healthy" group included samples from animals (n=40) and humans (n=7) without any signs of respiratory disease.

The nasal secretion samples were measured by frontal input mode under static conditions due to spontaneous diffusion of vapors into the near-sensory space of the detection cell from biosamples.

3. Results and Discussion

3.1. Microstructural Investigation of Hydroxyapatite Phases

The microstructure of HA coatings of different mass was investigated by atomic force microscopy with a video surveillance system to understand the features of the sorption properties (Fig. 2). Based on the images obtained in the Nova 1.0.26.143 program (freely available), the average grain diameter and roughness were calculated (Table 1).

Table 1. Microstructural characteristics of HA coatings.

Mass of coating, μg	Average diameter of grain, nm	Roughness, nm
2.03	415	544
4.17	215	111
5.03	187	97

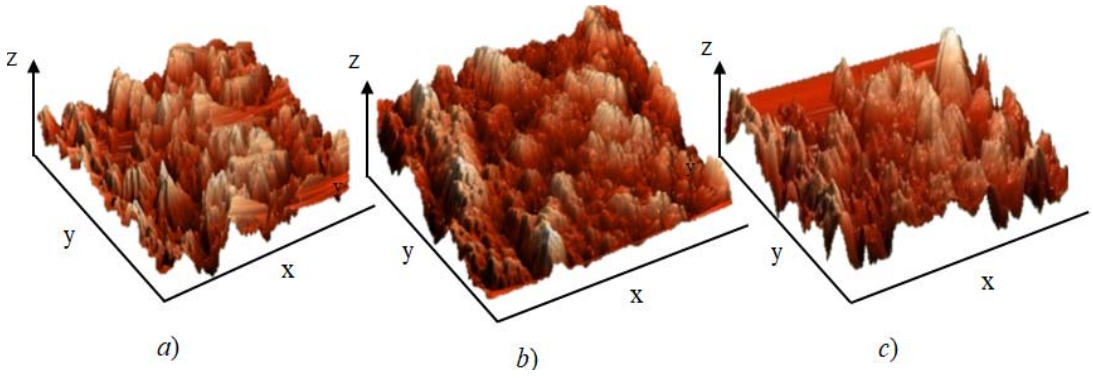

Fig. 2. Image of HA phases obtained in Nova program using AFM with resolution: 30×30 μm. Mass of HA m=2.19 μg (a); 4.17 μg (b); m=5.03 μg (c).

It was found that for HA with an increase in the coating mass, the average grain diameter and roughness decrease. It turns out that for coatings of HA with a different mass, a surface of different porosity is formed, which determines the variation in sorption properties of the coatings. It was also found that an increase in the mass of the HA coating by more than 4 μg does not lead to significant changes in the average grain size on the surface and roughness. This makes it possible to predict reproducibility and similar sorption properties with insignificant changes in coating weights of more than 4 μg, which is important for the industrial production of sensors with reproducible, repeatable properties.

3.2. Sorption Properties of the Hydroxyapatite Phase of Different Masses

Earlier it was established on the example of solid-state sorbents of different nature [14, 20-21] that an increase in the mass of phases on the electrodes of piezoelectric resonators has a different effect on the sensitivity of microweighing of water vapors and organic compounds. The dependence of the rate of change in the maximum sensor response on the mass of the hydroxyapatite phase on the electrodes was studied using several biomolecules of different polarity and injection input mode (Fig. 3).

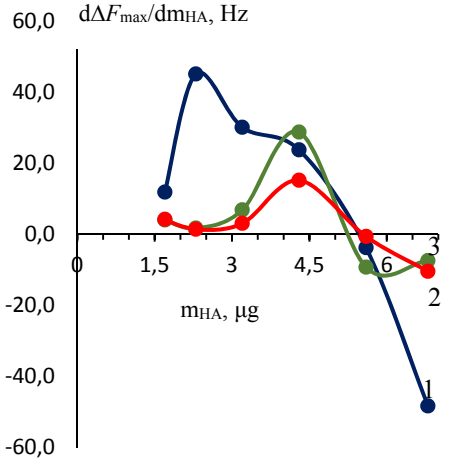

Fig. 3. Dependence of the rate of change of the maximum response of sensors on the mass of HA on the electrodes in vapors: water (1), ethanol (2), acetone (3).

The rate of change in the analytical signal per unit mass of the HA phase is proportional to the rate of sorption of analytes for a fixed time of loading the system. The rate of change in the analytical signal of the sensor in the vapors of all three compounds depends on the mass of HA, but in different ways for water and organic biomolecules (ethanol, acetone). Phases of small masses (1-2 μg) and big (more than 5 μg) react equally ineffectively to vapors of all compounds. The highest rate of change in the signal of a sensor with 2.0-3.5 μg mass HA is characteristic of water vapor, while the sensor reacts slowly to organic compounds in this mass range. The rate of change in the analytical signal of the sensor for all compounds is equal for sensors with a 3.5-5.5 μg HA phase.

Nevertheless, varying the coating mass is more critical for weighing water vapor than for ethanol and acetone. This fact is helpful in microweighing the vapors of biomolecules of organic compounds against the background of water. Furthermore, using two sensors with a small and big mass of the HA phase makes it possible to separately indicate ethanol and acetone vapors in a sample with any concentration of water vapors. This approach allows us to speak of separate microweighing of biomolecules without separation by at least two sensors with HA phases.

Further, to study the sorption properties of HA coatings, sorption isotherms were constructed and studied (Fig. 4). The isotherm shape for HA phases of different masses changes from linear to S-shaped for the same sorption system. In this regard, it is impossible to describe the curves by a single theory: linear isotherms were described according to Langmuir's theory and S-shaped by polymolecular adsorption theory (BET-theory) (Table 2).

Based on the obtained results, an increase in adsorption (a) is observed in the homologous series of alcohols C_2H_5OH-$C_5H_{11}OH$ during sorption on the HA. At the same time, the number of adsorbed centers per unit mass of the adsorbent increases, and due to this, the sorption process proceeds much better. Using calculated monolayer capacity, it can be concluded that the HA phase exhibits the best sorption properties to water, propanol-1, butanol-1.

It is challenging to analyze the peculiarities of the mechanism of interaction of even homologues on the same sorbent phase using the obtained isotherm. The differences in the character of isotherms for one sorbent with different characteristics of the surface make it possible to estimate changes in the filling of pores of different nonideal phase geometry. Henry coefficient K_a, Hz*dm^3/mol is a priority characteristic of the systems under consideration since it characterizes the sensitivity of piezoelectric sensors to a particular type of vapor (Table 2). It was found that the values of the K_a coefficient for water vapor, butanol-1 depend on the mass of the sorbent phase, while for other compounds, within the limits of the microweighing sensitivity error, they are indistinguishable or change insignificantly. The affinity for butanol-1 molecules changes especially sharply in the HA phases of small (1-2 μg) and large masses (4-5 μg). If we take into account that the roughness of the surface of the HA phase also changes sharply (Table 1), it can be argued that for a linear alcohol molecule the surface parameters are defining the sorption character.

The sensitivity of microweighing increases with an increase in the number of carbon atoms in the alkyl radical of alcohol. A decrease in the polarity of alcohol molecules with an increase in the length of the alkyl radical reduces the effect of hydrogen bonds during sorption, but at the same time, it is on the rougher surface of low-mass phases that heavy alcohols are more efficiently sorbed. The obtained correlation for alcohols is stable and is consistent with the theoretical foundations of piezoelectric quartz microweighing. The nature of the change in the sensitivity of piezoelectric balances with low mass HA allows predicting an increase in sensitivity with further growth of the alkyl radical in the alcohol molecule.

For a sorbent phase of small masses (2-3 μg), the sensitivity of microweighing of vapors of substances decreases in the following sequence: alcohols> acetone> water> diethylamine> benzene.

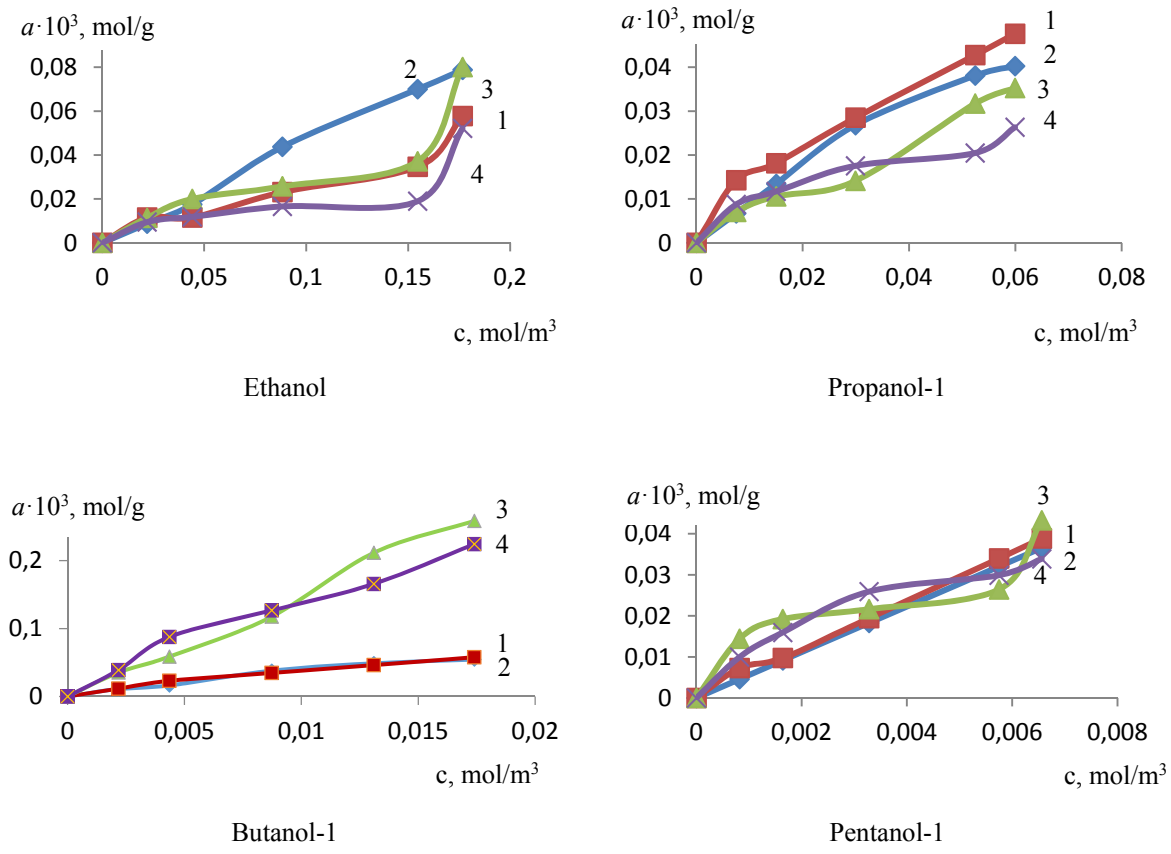

Fig. 4. Isotherms of alcohols vapor sorption on the HA phases of different mass: 1 – m=1.03 μg; 2 – m=2.19 μg, 3 – m=4.17 μg; 4 – m=5.03 μg.

Table 2. Constants of sorption isotherm of volatile compounds on the HA coatings with different mass.

Sorbtives	Lengmuir's model		BET theory	
	Mass of coating, m_{HA}, μg	Henry coefficient K_a, Hz·dm³/mol	Mass of coating, m_{HA}, μg	Constant C_{BET}, dm³/mol
Water	1.03 2.15	6.4 2.0	4.17 5.03	32 16
Ethanol	2.15	4.5	1.03 4.17 5.03	5.4 8.9 20
Butanol-1	1.03 2.15 4.03 5.03	36 35 15 13	-	-
Butanol-2	1.03 2.15	12 10	4.17 5.03	38 57
Pentanol-1	1.03 2.15	59 56	4.17 5.03	98 34
Acetone	1.03 2.15	0.7 0.8	4.17 5.03	2.1 1.4
Diethylamine	2.15 4.03 5.03	0.4 0.4 0.2	1.03	1.1

For sorbent phases of big masses (4-5 μg), the efficiency of microweighing decreases in the following order: phenol >> alcohols C_4-C_5 > water > chloroform > ethanol, acetone > benzene > diethylamine.

The mass sensitivity sequences for the small and big mass phases of biohydroxyapatite are not identical. This confirms the participation in sorption not only of the chemical sorption centers but also of pores, channels, and rough surfaces of HA phases to a greater

extent than for carboxylated carbon nanotubes and polymer sorbents [22-23].

The method of vapor input (injection or frontal) also significantly affects selectivity. It was found that with the injection of vapors of the studied compounds, the HA phase with a mass of 4-5 μg is most selective to vapors of ethanol, acetone, amines, amyl acetate, and acids, and the phase with a mass of 2-3 μg is most selective to vapors of methylamine, benzylamine, and acetic acid. In the frontal mode of vapor input, selectivity was noted for many biomolecules upon sorption on the small mass HA phase than on the big mass HA phase.

The possibility of identifying the studied vapors of substances with simultaneous microweighing with piezoelectric balances with different masses of the HA phase has been demonstrated in Table 3. The parameters of the sorption efficiency A(i/j) [8, 18] were calculated for sensors with the HA phase of different masses – A_m(i/j), where i, j are the mass of the phase (μg). In Table 1, the values of the parameters of the sorption efficiency are highlighted in bold, which can be used to solve problems of identification of individual substances in a mixture and correspond to requirements for identification parameters [8-9]. Thus, the identification parameters for water and phenol is the parameter A_m(i/j) for sensors with HA phase of small masses (1 and 3 μg). The simultaneous use of a small (1 μg) and a big mass (4-5 μg) of the HA phase makes it possible to identify propanol-1 and benzene in the mixture (Table 3).

Table 3. Parameters of the sorption efficiency of vapors (A_m(i/j)) of substances on piezoelectric balances with a HA phase of different masses in the injection mode.

Analytes	Values of HA mass in μg for parameter A_m(i/j)				
	1/2	1/4	1/5	2/4	4/5
Water	**3.2**	0.20	0.40	**0.06**	1.6
Ethanol	1.2	0.61	0.27	0.51	0.45
Propanol-1	1.1	0.86	**0.14**	0.80	**0.16**
Propanol-2	2.0	0.52	0.91	0.26	1.8
Butanol-1	1.0	0.24	0.28	0.23	1.2
Butanol-2	1.2	0.32	0.21	0.26	0.67
Pentanol-1	1.1	-	-	-	0.67
Benzene	0.95	**1.1**	2.1	1.1	2.0
Phenol	**0.69**	0.79	1.7	1.1	2.2

The mode of vapor injection into the detection cell significantly changes the identification parameters of biomolecules. A_m(4/2) identification parameters were calculated for 2 μg and 4 μg masses of the HA phase at the injection and frontal input mode (Table 4).

The overlap of the identification parameter values using the coincidence criterion [9, 18] at different modes of vapor input was established for water, acetone, benzene, methylamine, ethylacetate, and acetic acid (Table 4). The differences are significant for other compounds, and the identification parameters obtained under different sorption conditions cannot be applied. It is explained the different character of dependence of the sensor signal on the concentration of the analyte in the detection cell and near sensory space. Vapors of acetone, benzene, methylamine, ethyl acetate, acetic acid have a linear dependence of the sensor signal on the concentration of the substance in the studied range. For vapors with nonlinear dependence of the sensor signal on the concentration of the substance (alcohols, phenol, chloroform, diethylamine), the differences in the values of the parameters are significant.

Table 4. Parameters A_m(4/2) with injection and frontal mode of vapors input into detection cell, F_0 = 10.0 MHz.

Analytes	Injection input mode	Frontal input mode	Coincidence criterion
Water	1.0	1.1	0.3
Ethanol	0.25	0.52	0.08
Propanol-1	0.40	0.70	0.12
Propanol-2	0.38	1.3	0.26
Butanol-2	0.33	0.65	0.12
Pentanol-1	0.29	0.90	0.16
Acetone	0.25	0.17	0.09
Methylethylketone	1.00	0.55	0.14
Benzene	0.45	0.31	0.15
Phenol	0.25	0.74	0.14
Chloroform	0.43	1.5	0.28
Methylamine	2.5	1.7	0.9
Diethylamine	0.08	0.54	0.12
Ethylacetate	0.88	1.1	0.24
Acetic acid	1.2	1.5	0.6
Butyric acid	0.40	0.18	0.12

The results correspond to the theoretical and practical foundations of sorption interactions. Therefore, an approach for identifying individual analytes in a mixture by comparing the identification parameters of standard test substances and calculated for analyzed samples obtained under identical experimental conditions is acceptable.

The frontal mode of vapors input allows identifying more substances in the mixture than the injection input. For the analysis of biosamples, comparison of their state, and assessment of changes in time, the most promising is the frontal input mode of highly volatile compounds, which significantly simplifies the experiment and practically eliminates sample preparation.

3.3. Nasal Secretion Analysis

Clinical examination and analysis of biological samples by laboratory methods made it possible to classify animals by the degree of damage to the respiratory organs [7, 9]. The array included sensors with phases of biohydroxyapatite of different masses (4.0 μg and 2.0 μg). According to the measurement results, the values of the parameter A_m(4/2) were

calculated for 50 samples of nasal secretions of calves and the informative values of this parameter for ranking into groups "healthy", "inflammation" from the respiratory organs were found out (Table 5) with an assessment of classification errors for the systems with a binary response [24]. The numerical values of the calculated parameter $A_m(4/2)$ for sensors with HA phases help to identify individual test substances in samples and divide them into groups (Tables 4, 5). It was found that only for one range of values of this parameter, the proportion of false-positive assignments of samples from the "healthy" group to the "inflammation" group is equal to zero. For nasal secretion samples of the "inflammation" group, volatile compounds were identified (amines, alcohols, ketones, arenas). These compounds are markers of inflammation and protein destruction [8].

The versatility of the approach to assessing the state of the upper respiratory tract using highly volatile compounds of human nasal secretion was tested on 17 samples. In this case, the ranking of the samples into the "inflammation" group was carried out according to the range of the parameter $A_m(4/2) = 0.60 – 0.67$ (Table 6).

Table 5. Parameter $A_m(4/2)$ with the frontal mode of vapors input from nasal secretion samples of calves, $F_0 = 10$ MHz.

Calf stock number and diagnostic group	**Range of parameter $A_m(4/2)$ values**	**Identified compounds**	**Proportion of correct positive (false negative) answers**	**Proportion of correct negative (false positive) answers**
"Healthy": 2663, 2661, 2655, 2432, 2657, 2650, 2438, 2671, 2670, 2669, 2666 "Inflammation": 2646	0.77 – 0.9	No compounds dominating in concentration	- (0.1)	0.28
"Healthy": 2428, 2659, 2658, 2661, 2675 2443, 2437, 2659, 2667, 2662, 2647, 2668, 2657, 2664, 2653, 2442, 2662, 2676, 2677, 2674, 2679, 2675, 2674, 2673 "Inflammation": 2439, 2665, 2469	1.0 – 1.4	Propanol-2	- (0.3)	0.6
"Healthy": 2652, 2430, 2653, 2652, 2679 "Inflammation": 2672	1.5 – 1.8	Methylamine, acetic acid	- (0.1)	0.12
"Healthy": - "Inflammation": 2666, 2660, 2665, 2669, 2663	**0.60-0.67**	Diethylamine, ethanol, propanol-1, butanol-2, phenol, methylethylketone	0.5	- (0)

Table 6. Classification of human nasal secretion samples by parameter $A_m(i/j)$ for two sensors with 2 and 4 μg of HA.

Sample number	**Value of parameter $A_m(4/2)$**	**Assignment to the "inflammation" group according to the values of the parameter $A_m(4/2)$**	**Condition based on clinical examination**
1	0.63	Yes	Inflammation
2	0.63	Yes	Healthy
3	0.59	Yes	Inflammation
4	0.20	No	Healthy
5	0.63	Yes	Inflammation
6	0.67	Yes	Inflammation
7	1.0	No	Dry nose, secretion is almost absent
8	0.71	Yes	Healthy
9	0.83	No	Healthy
10	0.63	Yes	Inflammation
11	0.63	Yes	Inflammation
12	0.67	Yes	Inflammation
13	0.63	Yes	Inflammation
14	0.67	Yes	Inflammation
15	0.63	Yes	Inflammation
16	0.91	No	Healthy
17	0.77	No	Healthy
-	0.77	-	Water
-	1.0	-	Container

The proportion of correct ranking of human secretions samples in the "inflammation" group according to the selected numerical boundaries of the parameter $A_m(4/2)$ is 0.91. The proportion of false attribution for the considered sample is 0.25 due to the small size of the sample. However, the high sensitivity of assigning samples to the "inflammation" group confirms the correctness and versatility of the approach. The first and second order errors have been estimated in binary classification based on sorption parameters for sensors with HA. The sensitivity and specificity of classification were 100 and 86 %, respectively.

4. Conclusions

The study of the sorption of organic compounds and water vapors by phases of hydroxyappatite of different masses on the piezoelectric resonators is allowed to formulate a new approach to changing the selectivity of microweighing of VOCs.

A new identification principle in "electronic nose" system is proposed using one effective sorbent of different masses to identify VOCs in a mixture without separation.

The frontal mode of vapors input creates conditions similar to gas chromatography to recognize components in a mixture with a much simpler and faster instrumental solution.

The proposed sorption parameters could be applied to rapidly assess the inflammation presence in the upper respiratory tract of animals and humans. The correctness of the interpretation of the results was confirmed by the clinical examination and laboratory analysis results. The success of applying the approach in the analysis of biological samples of animals and humans opens up new prospects for out-of-laboratory diagnostics.

Acknowledgments

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