Methane and Hydrogen Gas Calibration Device for Medical Breath Tests

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Abstract–**The problems of medical breath tests exploitation were considered, and a method for solving these problems was proposed. A review of current systems and calibration methods was carried out. The benefits and deficiencies of these systems were highlighted. A non-standard method of preparation and calibration was described. A calibration device was provided to automatically prepare a standard test gas for calibrating medical respiratory sensors. Preparation errors of this device were quantitatively estimated and were 4% and 12.5% compared to commercially available device accuracy. Choice of the component to produce this device was provided.**

I. Introduction

Recently, the stomach microbiome was considered a fully functioning organ, whose health directly influences the human body. For example, research [1] shows that methanogens can cause Alzheimer's disease. Study [2] describes that the risk of developing obesity is related to M. smithii bacteria. The stomach microbiome during its growth produces methane and hydrogen. Afterward, these gases are eliminated from the body via blood and lungs. It was found that methanogens and hydrogen-producing bacteria have a symbiotic relationship [3]. Methane and hydrogen content in breath can serve as an indicator of show stomach microbiome health [4].

Hydrogen and methane breath analyzers are widely used in medical practice. According to the gas analyzer, diagnosis of carbohydrate intolerance (lactase deficiency, sucrase-isomaltase insufficiency) carbohydrate malabsorption, galactose and glucose malabsorption, small bowel bacterial overgrowth syndrome, exocrine pancreatic insufficiency, hepatic cirrhosis, constipation, coeliac disease and other can be done [5].

Today, the maintenance of medical gas analyzers is a complex and unresolved challenge. The gas sensors must be daily, weekly, or monthly calibrated to provide high metrological characteristics [6].

The most known traditional calibration method is the use of pressure bottles with calibrations gas (typical industrially manufacturing). These bottles contain gas at known concentrations. Various concentration ranges require more pressure bottles. Calibration through a gas cylinder limits the number of calibration points, that influence the quality of analysis. Pressure bottles must be first safely stored and maintained. As a result, it is difficult to automate the calibration process and create barriers to the introduction of medical breath tests for mass individual use. In addition, target gas concentration may change over time due to leaks or chemical interactions [7].

II. Commercially – available calibration devices

A device, which performs gas calibration through standard gas mixing. This device dilutes a standard gas mixture to generate various concentrations of the calibration gas. For example, dilution calibrator GGS-03-03 (ГГС-03-03, ООО “Monitoring“, Russia) [8]. Such a generator can reduce the number of gas cylinders.

Gas generators with microflow gas sources, for example, GDP – 102 (ГДП – 102, FSUE "SPA "Analitpribor", Russia) [9], are also in use today. A Microflow source is a vessel with permeable walls, that contain pure liquid gas or liquid. During blow, gas diffuses from this vessel at a constant speed. The major flaw of devices with microflow gas sources or dilution calibrators is the necessity of gas cylinders presence.

The market has systems such as UK – 01 (УК – 01, “Alfa Bassens”, Russia) which generates hydrogen calibration gas through mixing of a fixed value of air and target value of pure hydrogen [10]. Gaseous hydrogen is released in the chemical reaction of dissolution of metallic zinc in dilute sulfuric acid $Zn + H_2SO_4 \rightarrow ZnSO_4 + H_2$. This process involves a complex manual procedure of weighing a zinc metal using a microchemical balance. Such devices do not require a calibration gas cylinder but do not solve the problems of simplification and automatization of the calibration process for the end-user.

Another existing device [11] allows the preparation of a calibration mixture of zero-point gas through incineration of atmosphere air and again uses target gas for a lot of calibration cycles. This device does not need a calibration gas cylinder but works correctly only for zero-point.

Besides, a similar device exists which can calibrate gas sensors without wasting calibration gas. For example [12], such a device can use an infrared beam passed through optic fiber and a transparent sealed vessel with a certain concentration of target gas and then hit the calibrated optic gas sensor. However, this method is good only for optic methane sensors and is not suitable for medical purposes.

A method of obtaining the hydrogen gas using electrolysis of water [7] is known. This method allows the preparation of hydrogen calibration gas using solid-state electrolysis. However, this method is not available for methane and requires maintaining a high temperature of the unit.

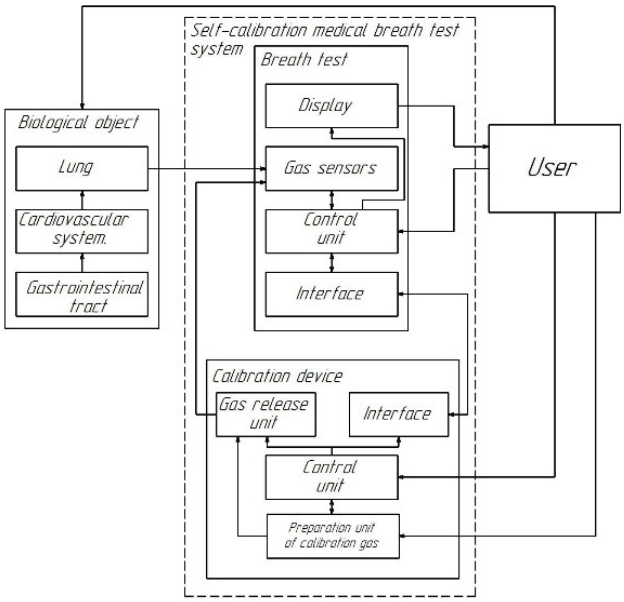

Fig. 1. Self-calibration bioengineering system for the medical breath tests

Based on the above considerations, there is a problem of developing a hydrogen and methane calibration device that will enable conversion from gas calibration cylinders to other technologies.

The calibration device (Fig. 1), presented in this work, meets the requirements of the automation challenge of medical breath test sensors in research such as [13]. Such studies require maintaining high metrological characteristics for a time. The device will help to simplify and automate the calibration process, which currently requires certain competence of the operator, and simultaneously can be portable enough to be integrated into a breath analyzer.

III. Method for producing methane and hydrogen

There are several ways to produce hydrogen. These are electrolysis in different electrolysis cells [14,15, 16] $2H_2O \rightarrow 2H_2\uparrow + O_2\uparrow$, obtaining hydrogen from the hydrides [17] $MHn + H_2O \rightarrow M(OH) + H_2\uparrow$, or metal hydration [11] $Al + 3H_2O \rightarrow Al(OH)_3 + 1.5H_2\uparrow$, hydrogen also can be obtained in a special electrolytic cell such as [18]. In addition, hydrogen is formed by mixing some metals with acids.

The methods of methane-producing are production from single substances reaction $C + 2H_2 \rightarrow CH_4$, from synthesis gas $CO + 3H_2 \rightarrow CH_4 + H_2O$, from a mixture of sodium acetate and sodium hydrate $CH_3COONa + NaOH \rightarrow Na_2CO_3 + CH_4\uparrow$, by hydrolysis of aluminum carbide $Al_4C_3 + 12H_2O \rightarrow 4Al(OH)_3 + 3CH_4\uparrow$ or Grignard reagent $CH_3MgI + H_2O \rightarrow CH_4\uparrow + Mg(OH)I$.

IV. Proposed calibration device

In the proposed device (Fig.3) calibration gases will be prepared from liquid reagents and ambient air by mixing two gas flows at a specified proportion. Mixing results in the flow of calibration gas for examination of medical breath test gas

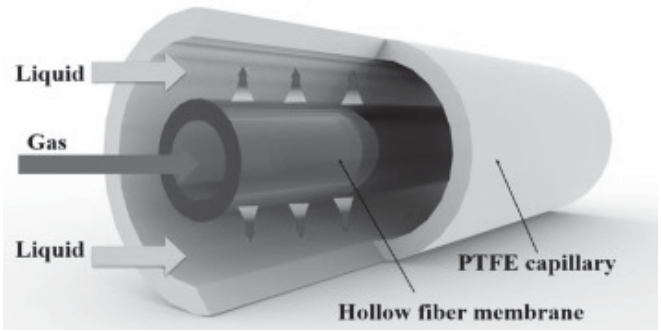

Fig. 2. Tube in tube microreactor [17]

sensor. The functional block diagram is shown in Fig. 2. The working principle is described on the example of methane.

Methane is produced in the “tube in tube” microreactor [17]. This reactor is composed of an internal tube made from a hollow fiber membrane and an external tube made from polytetrafluoroethylene (PTFE). Reagents are placed in an external tube, and products are released in the internal capillary (Fig. 1).

The advantages of reacting in microreactor are high-rate coefficients for reactions, safety, simplified automatized process, pure end-product, and good repeatability and reproducibility [18]. Microreactors can prepare explosive gases excluding transportation and storage [17].

Mixing Grignard reagent with water methane results in gas methane diffusing through a semi-permeable membrane into the internal capillary. Hydration of Grignard reagent is an exothermic reaction and proceeds violently [22]. As methane is nearly insoluble in water and ether, so it easily diffuses through the liquid and internal capillary.

Different concentrations of the calibration gas are obtained from two different simultaneous dilution principles. The first principle is flow dilution and the second is flow direction modulation. Modulation is the control flow of target gas or predilution mixed gas to accumulate flexible vessel or outflow to the atmosphere with a certain pulse ratio or duty cycle. To achieve low concentration two dilution cycle is implemented.

Flows are fixed on certain levels using a control system with feedback. Gas is pumped to the inlet of the critical orifice, and there is a mounting pressure and temperature sensor. The sensor helps to read the information on flow conditions and then the control device adjusts the capacity of the stream. Therefore, at inlet maintained fixed pressure, and the outlet of the critical orifice maintained fixed gas flow.

A critical orifice allows for definite mass flow through an orifice of a certain diameter at a given pressure at the inlet. Flow depends only on gauge pressure (Fig. 4).

Herewith consider the temperature according to equation 1 [23]:

$$Q_T = Q_s \sqrt{\frac{T_s}{T_T}} \quad (1)$$

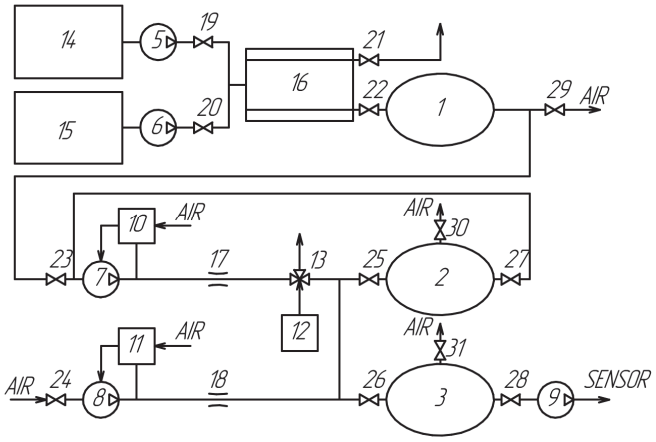

Fig. 3 Function block diagram of the calibration device.

And different gases according to equation 2 [23]:

$$\text{Flow(gas)}=\frac{\text{Flow(air)}}{\sqrt{\text{S.G.}}} \quad (2)$$

In (1), Q_T is a flow at a different temperature, Q_S is an experimentally obtained flow, T_T is a standard absolute temperature, T_S is a different absolute temperature, S.G. is the specific gravity of gas relative to air.

Block diagram of the proposed device is shown in Fig. 3, where 1–3 are sealed flexible volume, 5,6 and 7–9 are liquid and gas pumps respectively, 10–12 are control devices with pressure and temperature sensors, 13 is a three-way valve, 14 and 15 are the volumes with a liquid reagent such as water and Grignard reagent, 16 is a tube in tube microreactor, 17 and 18 is a critical orifice, 19 and 20 are normally open liquid valve, 21–31 are normally open gas valve, AIR mean communication with the atmosphere, SENSOR mean outlet for calibration sensor

A device shown in Fig. 3 operates as follows. It prepares clear target gas in the microreactor and then dilutes it to the necessary concentration in one or two dilute cycles. Dilution takes place at two controlled gas flows. Herewith flow is managed via pump pressure and temperature sensor and controller, which fixed it on a certain level.

For example, by mixing a target gas flow with 24.5 cm^3/min [23] and a diluent airflow with $2.62 \cdot 10^{-3}$ cm^3/min [23], we obtain a dilution of about 1/100 in one cycle in volume 2. After that, it can repeat dilution from volume 2 to volume 3. The volume will have the target gas at 1/10,000 or 100 ppm dilution without using flow modulation. If you modulate the flow at each dilution step by diluting at 1/10, we get a dilution of 1/100 in two steps with a resulting 1/1,000,000, or 1 ppm.

Therefore, if you dilute the target gas with modulating, then you will have obtained calibration gas with a concentration of 1 to 100 ppm. This corresponds to the necessary concentration rate of an already known gas in human breath and the rate for medical hydrogen and methane breath analyzers.

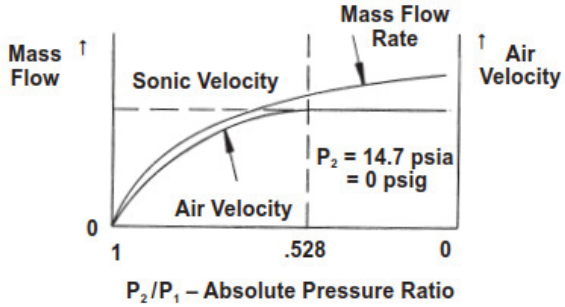

Fig. 4. Relationship between pressure and air mass flow through orifice [23]

The algorithm operates as follows (Fig. 3):

Algorithm 1 Preparations methane calibration gas

0: At first, sealed bag 1 and internal capillary 16 are evacuated via pump 7 and valve 13. They prepare a volume for the target gas in this manner.
1: Pumps 5 and 6 from tanks 14 and 15 pump reagent into microreactor 16. The volume of reagents must be chosen so that they refresh the volume of the capillary. The flow was controlled through valves 19, 20.
2: The interaction of Grignard reagent with water results in the formation of methane. Methane fills internal capillaries in microreactor 16 and volume 1 through open valve 20 which is set in the volume of atmospheric pressure.
3: Then, pump 7 pumps target gas into volume 2 via critical orifice 17, and flow control is accomplished via manage device 11, which includes a pressure sensor and a temperature sensor. The controlling device read temperature and pressure properties at the inlet of the critical orifice and then adjusted the capacity of the stream so that flow at critical orifice outlet 17 was at a fixed level.
4: Simultaneously, in addition to operating pump 8, it controls device 11, which includes temperature and pressure sensors at the critical orifice's inlet 18. They create a fixed flow of atmospheric air, which here is diluent gas. Valve 25 and 30 are now open. Volume 2 is progressively filled in the low concentration of target gas. Flow is fixed at a certain pressure and a certain diameter of the critical orifice.
5: Here, control device 12 with three-way valve 13 modulates target gas flow, directing the stream either to the accumulated volume or to the atmosphere based on the required concentration in the dilution result. The first stage is completed, the valves 23, 25, and 30 are closed, and volume 2 contains prediluted calibration gas.
6: After that, valves 26, 27, and 30 open and, if you already know the method, dilute the prediluted calibration gas from volume 2 with atmospheric air and fill volume 3. Flow with prediluted calibrated gas fixed at critical orifice 17, the control device 10 includes pressure and temperature sensors, which operate gas pump 7 and modulate with required duty factor via commutation of the three-way valve 13 diluted with airflow through components 8,11, and 18.

AIR FLOW — SCCM

	Orifice Diameter (In.)	.0003	.0005	.0007	.0010	.0015	.0020	.0025	.0030	.0035	.0040	.0050
	Size Number	0C	0E	0G	1	1E	2	2E	3	3E	4	5
	Cv	.0000019	.0000053	.0000104	.0000216	.0000477	.0000840	.0001300	.0001860	.0002580	.0003490	.0005450
Supply Pressure — psig	5	0.50	1.38	2.70	5.60	12.4	20.9	33.8	48.2	67.9	90.6	144
	10	0.72	2.00	3.92	8.13	18.0	31.3	49.4	70.6	97.1	133	203
	15	0.90	2.51	4.92	10.2	22.2	40.2	62.6	88.7	123	164	253
	20	1.08	2.99	5.86	12.2	26.7	47.7	74.5	108	146	194	299
	25	1.24	3.44	6.74	14.0	31.0	55.0	86.0	124	168	220	344
	30	1.40	3.90	7.64	15.9	35.3	62.1	97.3	141	190	250	390
	40	1.74	4.83	9.47	19.7	43.8	77.4	123	173	233	309	482
	50	2.09	5.80	11.4	24.5	53.2	92.1	146	204	278	369	570
	60	2.42	6.73	13.2	28.4	61.8	107	169	237	324	428	662
	70	2.76	7.65	15.0	32.5	70.2	121	192	270	369	487	753
	80	3.09	8.57	16.8	36.5	78.9	135	215	303	415	542	845
	90	3.45	9.56	18.7	40.7	87.4	153	241	337	461	602	938
	100	3.80	10.6	20.9	44.8	96.1	168	269	371	504	662	1036
	Flow Accuracy @ 25 psig	±0.40 SCCM	±0.50 SCCM	±0.60 SCCM	±0.70 SCCM	±1.5 SCCM	±4 SCCM	±6 SCCM	±8 SCCM	±10 SCCM	±20 SCCM	±20 SCCM

Fig. 5. Relationship between flow rate pressure and diameter of critical orifice, where SCCM - Standard cu. cm. per min. or cm^3/m [23]

Metal Orifice Air Flow – SLPM

	Orifice Diameter Inches	0.004	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021	0.022	0.023	0.024	0.025	0.026	0.027	0.028	0.029	0.031	0.032	0.033
	Size Number	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	31	32	33
	C_v	0.00035	0.00061	0.00086	0.0012	0.0015	0.0019	0.0025	0.0028	0.0034	0.0038	0.0043	0.0050	0.0055	0.0067	0.0073	0.0080	0.0088	0.0096	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.022	0.024	0.025
Supply Pressure – psig	1	0.035	0.064	0.086	0.127	0.170	0.226	0.280	0.308	0.398	0.45	0.52	0.61	0.66	0.77	0.86	0.96	1.05	1.13	1.29	1.41	1.54	1.67	1.91	1.95	2.21	2.39	2.65	2.88	3.03
	5	0.09	0.16	0.21	0.30	0.40	0.52	0.65	0.71	0.92	1.06	1.21	1.41	1.54	1.76	1.98	2.22	2.47	2.65	2.97	3.24	3.53	3.83	4.34	4.44	4.94	5.31	5.86	6.42	6.80
	10	0.12	0.22	0.31	0.43	0.57	0.74	0.93	1.01	1.29	1.48	1.68	1.95	2.01	2.26	2.54	2.83	3.16	3.53	4.33	4.75	5.18	5.55	6.15	6.43	7.18	7.83	8.63	9.40	9.98
	15	0.16	0.28	0.39	0.54	0.72	0.93	1.17	1.26	1.62	1.85	2.10	2.44	2.50	2.85	3.23	3.57	4.01	4.41	5.35	5.93	6.43	6.95	7.58	7.95	8.78	9.58	10.6	11.6	12.3
	20	0.19	0.33	0.46	0.65	0.85	1.10	1.38	1.49	1.92	2.19	2.49	2.87	2.97	3.40	3.86	4.26	4.84	5.22	6.35	6.95	7.58	8.15	8.90	9.28	10.3	11.2	12.4	13.5	14.3
	25	0.22	0.39	0.53	0.75	0.98	1.27	1.59	1.71	2.20	2.50	2.86	3.28	3.42	3.92	4.45	4.91	5.59	6.01	7.30	7.95	8.65	9.38	10.2	10.7	11.7	12.8	14.2	15.4	16.3
	30	0.25	0.44	0.60	0.85	1.12	1.43	1.80	1.93	2.47	2.82	3.21	3.69	3.87	4.43	5.03	5.56	6.33	6.81	8.23	8.98	9.75	10.6	11.5	12.0	13.2	14.4	15.9	17.3	18.4
	40	0.30	0.54	0.74	1.05	1.38	1.77	2.21	2.37	3.04	3.45	3.93	4.51	4.78	5.47	6.21	6.85	7.81	8.42	10.1	11.0	12.0	13.0	14.1	14.7	16.1	17.5	19.4	21.1	22.5
	50	0.36	0.65	0.88	1.26	1.65	2.10	2.62	2.80	3.58	4.07	4.64	5.31	5.70	6.51	7.40	8.15	9.26	10.0	11.9	13.0	14.2	15.4	16.6	17.3	19.0	20.7	22.9	25.0	26.6
	60	0.42	0.75	1.02	1.46	1.91	2.42	3.02	3.23	4.13	4.70	5.34	6.13	6.61	7.56	8.58	9.46	10.7	11.6	13.8	15.0	16.4	17.7	19.2	20.0	21.9	23.8	26.4	28.8	30.7
	70	0.48	0.86	1.16	1.67	2.17	2.75	3.43	3.66	4.68	5.32	6.05	6.96	7.53	8.61	9.77	10.8	12.2	13.2	15.6	17.0	18.5	20.1	21.7	22.7	24.8	27.0	30.0	32.7	34.9
	80	0.54	0.96	1.30	1.87	2.43	3.08	3.83	4.09	5.23	5.95	6.77	7.79	8.46	9.67	11.0	12.1	13.7	14.9	17.5	19.0	20.7	22.5	24.2	25.3	27.7	30.2	33.6	36.7	39.0
	90	0.60	1.07	1.44	2.08	2.69	3.40	4.23	4.51	5.78	6.58	7.49	8.62	9.38	10.7	12.2	13.4	15.2	16.5	19.3	21.0	22.9	24.9	26.8	28.0	30.7	33.5	37.2	40.6	43.2
	100	0.66	1.17	1.58	2.28	2.95	3.72	4.63	4.94	6.33	7.22	8.21	9.46	10.3	11.8	13.4	14.7	16.6	18.0	21.1	23.0	25.1	27.4	29.4	30.8	33.7	36.8	40.9	44.6	47.5
Vacuum Level In. Hg.	5	0.053	0.096	0.129	0.191	0.253	0.332	0.406	0.450	0.582	0.661	0.773	0.899	0.977	1.14	1.28	1.41	1.55	1.70	1.90	2.10	2.30	2.48	2.74	2.83	3.16	3.41	3.78	4.12	4.32
	10	0.069	0.124	0.168	0.246	0.324	0.421	0.519	0.564	0.730	0.834	0.972	1.12	1.24	1.41	1.58	1.79	1.96	2.18	2.44	2.68	2.89	3.13	3.44	3.58	4.00	4.30	4.77	5.16	5.43
Choked Flow	15	0.075	0.134	0.185	0.268	0.351	0.455	0.566	0.614	0.792	0.902	1.07	1.22	1.35	1.55	1.75	1.94	2.19	2.32	2.61	2.85	3.12	3.34	3.65	3.78	4.20	4.51	5.05	5.45	5.72
	20	0.075	0.134	0.185	0.268	0.351	0.455	0.566	0.614	0.792	0.902	1.07	1.22	1.35	1.55	1.75	1.94	2.19	2.32	2.61	2.85	3.12	3.34	3.65	3.78	4.20	4.51	5.05	5.45	5.72
	30	0.075	0.134	0.185	0.268	0.351	0.455	0.566	0.614	0.792	0.902	1.07	1.22	1.35	1.55	1.75	1.94	2.19	2.32	2.61	2.85	3.12	3.34	3.65	3.78	4.20	4.51	5.05	5.45	5.72

Fig. 6. Relationship between flow rate pressure and diameter of critical orifice, where SCCM – Standard Liters Per Minute. or 10^{-3} cm^3/m [23]

V. Overview of Available Components

As pumps 14 and 15 must be used pump with a small dosage volume. Micro annular gear pump mzr-2505 has a dosage volume of 0.25 cm^3. That would enable preciseness and economically consume reagents [24].

Gas pump BTX-Connect Single Head Compact BLDC Motor B1C has a small size. His flow rate is up to $9 \cdot 10^3$ cm^3/min [25]. This pump is used as pump 7,8,9 in Fig. 3.

As three-way valve 13 chosen BIBUS 320 series with a minimum response time of less than 1.5 ms [26].

Diameters of the critical orifice were chosen 0,0254 mm (size number 10 in Fig. 6) for target gas (item 17) and 0,254 mm. (size number 1 in Fig. 5) for diluent atmosphere air (item 18). Data in Fig. 5,6 was experimentally determined and provided by the manufacturer [23].

Capillary microreactor 16 is such as in research [20] with the following parameters presented in Table I:

Here, the length of the microreactor was 1 cm (50 times shorter than in research [20]). Then, inlet and outlet volumes were $V_1=9{,}498 \cdot 10^{-3}$ cm^3 and $V_2=0{,}96 \cdot 10^{-3}$ cm^3 [18] respectively.

As pressure sensor in the control of devices 10 and 11 will be Absolute and Gauge Pressure transducer Series 2000 with high accuracy of 0.01% [27]

VI. Estimate an Accuracy Calibration Device

A calibration of methane analyzer using Grignard reaction, errors occur at preparation target gas δ_1, pressure sensor error δ_2, uncertainty flow through critical orifice δ_3, and inaccuracy by three-way valve δ_4.

At the beginning of the reaction, internal capillary 12 and some volume in the sealed bag 11 have an unknown gas mixture, because gas evacuates incompletely. Take it into consideration as an error. Providing pressure into capillary equals the atmospheric.

TABLE I. TUBE IN TUBE MICROREACTOR DIMENSIONAL CHARACTERS

Capillary	Diam.	Value	Unit	10^{-3} cm^3/ cm
internal	internal	350	μm	0.96
	external	450	μm	
external	internal	1	mm	9.498
	external	Not provide		

Calculate the amount of a substance in this gas mixture from the equation 3:

$$\nu_{err}=\frac{P_{air}\times V_2}{R\times T_{air}}=0.23\times10^{-7}\text{mol} \quad (3)$$

where T_{air}=300 °K; $P_{air}=10^5$ kg/(m·s^2) are atmospheric temperature and pressure; R=8.31; ν_{err} is an amount of error gas.

Provide concentration of reactant CH3MgI = $3\cdot10^{-6}$ mol/cm^3 (commercially available methylmagnesium iodide [28]) the amount of methane after completing the reaction from equation 4:

$$\nu_{CH4}=3\times10^{-6}\ \text{mol/cm}^3\times\frac{V_1}{2}=142.47\times10^{-7}\text{mol} \quad (4)$$

where ν_{CH4} is the amount of target methane gas. The ratio of the reactant volume is 1:1.

This gas mixture is used in the following as target gas. Here the concentration of methane is from equation 5:

$$\frac{\nu_{CH4}}{\nu_{err}+\nu_{CH4}}\times100\%=99.2\% \quad (5)$$

It means δ_1= 0.8% error of preparation target gas mixture.

At normal pressure and temperature this gas will flood the volume from the equation 6:

$$V_{gas}=\frac{P_{air}\times(\nu_{err}+\nu_{CH4})}{R\times T_{air}}=571\ \text{cm}^3 \quad (6)$$

where T_{air}=300 °K; $P_{air}=10^5$ kg/(m·s^2) are atmospheric temperature and pressure R=8.31; ν_{err} is the amount of error gas; ν_{CH4} is the amount of target methane gas; V_{gas} is the volume of the gas mixture at normal pressure and temperature.

According to technical documentation [27] pressure sensor accuracy is δ_2=0.01%.

Critical orifice flows uncertainly accepted as from equation 7:

$$\delta_3=\frac{0.7}{24.5}\times100\% \quad (7)$$

where 0.7 cm^3/min is a flow rate error at a nominal flow rate of 24.5 cm^3/min at a certain condition: at 50 psig pressure and 0,0254 mm orifice diameter. This data in Fig. 5,6 was experimentally determined and provided by the manufacturer [23].

Inaccuracy by the three-way valve (1.5 ms response time) δ_4 was evaluated as the rate of difference between a rectangle and trapeze flow signal area to a rectangle flow signal area. The rectangle flow signal area is an ideal signal without a 1.5 ms uncertain time.

The trapeze flow signal is an approximate real signal with a 1.5 ms response time (Fig. 7). Herewith signal duration is 20 ms according to equation 8:

$$\delta_4=\frac{S_{rec}-S_{tra}}{S_{rec}}\times100\%=\frac{20\text{ms}\times1-\frac{20\text{ms}+17\text{ms}}{2}\times1}{20\text{ms}\times1}\times100\% \quad (8)$$

where S_{rec} is a rectangle area in Fig. 7 S_{tra} is a trapeze area in Fig. 7.

There is the worst-case accuracy δ of calibration gas preparation i.e., 1ppm calibration gas error according to GOST 12.1.016-79 is from the equation 9,10:

$$\delta=1.1\times\sqrt{\delta_1^2+2\times\delta_2^2+2\times\delta_3^2+2\times\delta_4^2} \quad (9)$$

Here coefficient 2 means two cycle preparation.

$$\delta=1.1\sqrt{0.8^2+2\times0.01^2+2\left(\frac{0.7}{24.5}\times100\right)^2+2\left(\frac{20-\frac{20+17}{2}}{20}\times100\right)^2} \quad (10)$$

And the best-case accuracy δ of calibration gas preparation i.e., 100ppm calibration gas error according to GOST 12.1.016-79 is from the equation 11,12:

$$\delta=1.1\times\sqrt{\delta_1^2+2\times\delta_2^2+2\times\delta_3^2} \quad (11)$$

$$\delta=1.1\times\sqrt{0.8^2+2\times0.01^2+2\times\left(\frac{0.7}{24.5}\times100\right)^2} \quad (12)$$

with coefficient 1.1 and confidence coefficient equal P=95%. The worst-case accuracy of calibration gas preparation equals 12.5%. The best-case accuracy of calibration equals 4.5%

This is less than the accuracy of the medical breath analyzer ±20 %, and less than physiological hydrogen and methane breath concentration variations ±10 %.

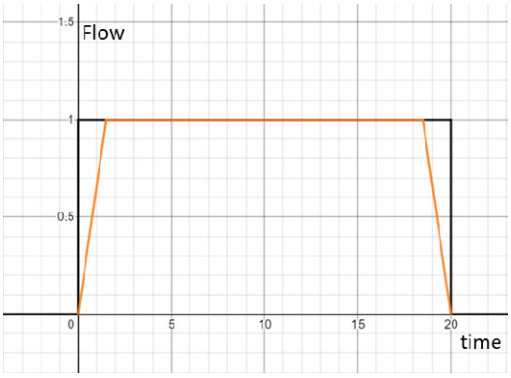

Fig. 7. Illustration of calculation δ_4.

VII. Conclusion

As a result, a device shown on the functional diagram (Fig. 3) would replace the need for a pressure bottle for calibration methane and hydrogen medical breath tests. Herewith the preparation error of this device is no more than 12,5%.Target gas in this mixture may vary from a few up to several hundred ppm, which enables calibration of the sensor with a nonlinear transfer function. The claimed device makes it possible to automate and simplify the calibration process and eliminate storing, buying and maintaining expensive and unwieldy pressure gas cylinders.

In comparison with a device such as dilution calibrator GGS-03-03 [8], the proposed calibrator does not need a calibration gas vessel and therefore it is more compact. The proposed device can prepare hydrogen target gas while a microflow gas generator like GDP – 102 [9] has no hydrogen microflow source solution. A system such as UK – 01 [10] could not be automatic in contrast proposed calibration device and in addition, it has less accuracy. Solution [7, 11, 12] in comparison proposed device can't calibrate simultaneous hydrogen and methane gas sensors. A comparison with existing systems is presented in Table II.

TABLE II. COMPARISON WITH ANALOGS [8,9,10]

Parameter	GGS-03-03	GDP–102	UK–01	Proposed device
Methane	Yes	Yes	No	Yes
Hydrogen	Yes	No	Yes	Yes
Other gas	Yes	Yes	No	Yes (with other reagents)
Accuracy	0,2 - 4%	8 - 12%	not provided	4-12.5%
Ratio	10^{-6} to 10^{-3} % (Volume ratio)	0,7 to 33 mg/m3 (Volume ratio is not provided)	3 to 10 % (Volume ratio)	10^{-6} to 10^{-4} % (Volume ratio)

References

[1] C. Chun, H.A. Eun, S.K. Seung, L. Xia, A. Ashfaqul, Y. Keqiang, "Gut dysbiosis contributes to amyloid pathology, associated with C/EBPβ/AEP signaling activation in Alzheimer's disease mouse model." *Science advances* vol. 6(31), Jul. 2020, pp. 4-66.

[2] R. Mathur, G. Kim, W. Morales et al., "Intestinal Methanobrevibacter smithii but not total bacteria is related to diet-induced weight gain in rats", *Obesity (Silver Spring),* Vol. 2 (4), 2013, pp. 748–754.

[3] T. Stadtman, "Methane fermentation", *Annu. Rev. Microbiol.,* 1967, pp. 121-142.

[4] M. Simren, P.-O. Stotser, "Use and abuse of hydrogen breath tests" *Gut*. 2006. pp. 297-303.

[5] M.A. Dmitrienko, I. E. Jahatspanian, "Choice of detectors for hydrogen-methane breath test", *Association of Medicine and Analytics*, Dec. 2016 pp. 42-46.

[6] Official website of FAN GmbH, Lactofan2 user manual, Web: https://fan-gmbh.de/wp-content/uploads/documents/lactofan2_manual.pdf.

[7] V.A. Koltygin, "Способ изготовления смесей для калибровки газоаналитического оборудования с использованием твердотельного электролизера", "The method of preparation calibration gas through solid state electrolyser", RU2661074C1, 2018.

[8] Official website of ООО «ТД «Автоматика», instruction handbook of ГГС-03-03 gas mixture generator, Web: https://www.gasdetecto.ru/files/330/GGS-03-03_generator_gazovyh_smesei_RE.pdf.

[9] Official website of ФГУП "СПО "Аналитприбор", technical information of ГДП – 102 gas analyzer, Web: https://www.analitpribor-smolensk.ru/products/poverka_gazoanalizatorov/gdp102_generator_gazov/.

[10] Official website of ООО «ТД «Автоматика», technical information of УК-01 calibration device, Web: https://www.gasdetecto.ru/files/330/uk-01-ustrojstvo-dlya-gra.pdf.

[11] M. Ozawa, H. Fukushima, S. Kurihara, T. Hirayama, "Hydrogen concentration measuring system, and method for calibrating hydrogen concentration measuring instrument", JP2011002396, 2011.

[12] G. Qinghua, "Self-calibration air chamber and distribution type fiber-optic methane sensing system", CN107238580A, 2017.

[13] D. Polag, F. Keppler, "Long-term monitoring of breath methane" *Science of The Total Environment*, May 2018, pp 69-77.

[14] V.N. Fateev, "Получение водорода электролизом воды", "Hydrogen production through water electrolysis", *Программа и труды Пятой Всероссийской конференции с международным участием Топливные элементы и энергоустановки на их основ, Program and proceedings of the Fifth All-Russian Conference with international participation Fuel cells and power plants based on them*, June 2018, pp. 16-18.

[15] S. Biswas, A. P. Kulkarni, S. Giddey, S. Bhattacharya, "A Review on Synthesis of Methane as a Pathway for Renewable Energy Storage With a Focus on Solid OxideElectrolytic Cell-Based Processes", *Frontiers in Energy Research*, Vol. 8, 2020, pp. 1-23.

[16] D. Wei, J. Shikui, G. Junbo, L. Lu, W. Xiaochen, L. Zhen, B. Chen, Z. Weijing, C. Junna, H. Chuncai, "A kind of Portable oxyhydrogen calibrating installation and method", CN110441474, 2019.

[17] K. Fujiwara, "Calibrating device for hydrogen gas sensor, and calibration method of hydrogen gas sensor using it", JP2008224643A, 2008.

[18] Official website of Varta-AG, technical information of Varta hydrogen micro battery, Web: https://www.varta-microbattery.com/en/products/hydrogen-generator-cells.

[19] A. Christopher, C. Hone, O. Kappe, "Membrane Microreactors for the On-Demand Generation,Separation, and Reaction of Gases", *Chemistry A European Journal*, Oct. 2020, pp. 13108-13117.

[20] M. Liu, X. Zhu, R. Chen, Q. Liaoa, Y. Dingding, B. Zhang, L. Jian, G. Chen, K. Wang, "Tube-in-tube hollow fiber catalytic membrane microreactor for the hydrogenation of nitrobenzene", *Chemical Engineering Journal*, Dec. 2018, pp. 35-41.

[21] N. Assmann, P. Rudolf von Rohr, "Extraction in microreactors: Intensification by adding an inert gas phase", *Chemical Engineering and Processing: Process Intensification*, Aug. 2011, pp. 822-827.

[22] J. Robert, J. Ouellette, D. Rawn, "Haloalkanes and Alcohols", *Organic Chemistry,* Jan. 2014, p. 1056

[23] Official website O'Keefe Controls CO. catalog with precision critical orifice, Web: https://www.okeefecontrols.com/wp-content/uploads/Cat.-11-Superseded.pdf.

[24] Official website of B2B Sourcing Platform Europages, technical information of High performance pump series mzr-2505, Web: https://www.europages.de/High-performance-pump-series-mzr2505/HNP-MIKROSYSTEME-GMBH/cpid-5832887.html.

[25] Official website of Parker Hannifin Corporation, technical information of Mini Pumps BTX-Connect series, Web: https://www.parker.com/Literature/Precision%20Fluidics/Miniature%20Diaphragm%20Pumps/PPF_Pumps_Catalog.pdf.

[26] Official website of BIBUS valve distributer, technical documentation of Matrix valve, series 320, Web: https://www.bibus.uk/products-solutions/pneumatics/valves/high-speed-valves/matrix-series-320.

[27] Technical documentation of SERIES 2000 Absolute and Gauge Pressure Transducers, Web: https://www.althensensors.com/media/27263/2000-ultra-high-precision-pressure-sensor-en.pdf.

[28] Website of reactant suppliers, Web: https://www.chemsyn.ru/magnijorganicheskie-soedineniya-reaktivy-grinyara/metilmagnijjodid-metiljodid-magniya.