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TOPICAL REVIEW

Ion mobility spectrometry coupled with multi-capillary columns for metabolic profiling of human breath

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Abstract

Recently, ion mobility spectrometry (IMS) started to be used for direct breath analysis with respect to metabolic profiling, biomarker finding and gas trace analysis. The present review describes the basic operation of an ion mobility spectrometer including the ionization process, humidity effects and sampling procedures. To enhance the resolution, pre-separation by multi-capillary columns (MCCs) is discussed and examples for IMS chromatograms are presented. The focus is to review the analytical method IMS with respect to potential use for direct investigations of humid air in direct breath analysis but not on detailed discussion of results of specific medical application of MCC/IMS or on specific analytes found in exhaled air.

(Some figures in this article are in colour only in the electronic version)

Introduction

During the 1990s, practical aspects and fundamental understanding of ion mobility spectrometry (IMS) underwent dramatic changes so that contemporary IMS may be largely unrecognizable, by any measure, from descriptions between 1970 and 2000 [1]. For example, the high successful transfer of a laboratory research tool to a hand-held field analyser, developed in 10 000 units and used in battlefield environments [2, 3], is unprecedented in the history of analytical instrumentation. There are a lot of activities worldwide associated with the adaptation of IMS to industrial and environmental applications [4–13]. New developments as the combination of IMS to pre-separation techniques such as gas-chromatographic columns [14–23] started. In recent years, the first applications of IMS came out with respect to applications in medical field [24–35].

One intention of this review is to summarize proven and promising advances of IMS technology and to highlight opportunities for medical uses, especially for investigation of human breath as a carrier of information about the state of health. After a brief general discussion, relevant facets of IMS will be critically discussed so that prospective users can make informed decisions on IMS for particular applications in different medical fields. The paper is not intended to provide a comprehensive review in general but addresses a question frequently posed by potential applicants: 'What principles underlie IMS and what can be gained with IMS in breath analysis over other laboratory techniques?' Thus, the papers will follow the pattern of operating principles, characteristics of response, sampling, coupling of pre-separation techniques, proven applications with respect to breath analysis and its future trends.

In the present review, conventional IMS coupled to a separation column (GC) should be considered. Other methods such as differential ion mobility spectrometry (DMS) [33, 36–43] or high-field asymmetric waveform ion mobility spectrometry (FAIMS) [44–59] are not considered, but

referenced. Examples are taken from own applications of IMS on breath analysis.

A general discussion of methods used in breath analysis was reviewed recently in Spectroscopy Europe [26, 60, 61] and will be summarized here only briefly. Today, a wide range of techniques are used for scientific medical investigations and clinical trials which include gas chromatography coupled to mass spectrometry; different mass spectrometric methods [26, 62–71] based on proton-transfer reactions, ion–molecule reactions or selected ion flow; and laser spectrometric methods [72, 73] including infrared cavity leak-out spectroscopy or tuneable absorption spectroscopy, partly in combination with quantum cascade lasers and different kinds of sensors for single molecule detection. Some of the methods need sampling in bags and some use pre-concentration techniques on granulated resins or SPME (solid-phase micro extraction) [74, 75].

One focus is to review ion mobility spectrometry as an analytical method with respect to potential use for direct investigations of humid air in direct breath analysis but not on detailed discussion of results of specific medical questions related to MCC/IMS [7, 14, 27, 28, 31, 32, 76–82] or on specific analytes found in exhaled air [61, 67, 68, 70, 71, 83–105]. The moisture content of exhaled breath samples is a major problem for most analytical methods, besides SIFT-MS and MCC/IMS [28]. Therefore, the effect of humid air with respect to MCC/IMS is considered in detail from the ionization process to the application of MCCs for pre-separation.

The development of the instrument is discussed and significant for the review. It is not a discussion about quantification of the different analytes in detail. The range of determination is generally different for each analyte and depends, e.g., on the ionization processes and some different parameters. Generally, the detection limit goes down to the ng L^{-1} and pg L^{-1} ranges also in humid air (ppb_v to ppt_v range). In addition, resolution or separation efficiency is not considered and specific details of tubing, mouthpieces, heating, purging, surface treatment, cleaning and decontamination are not discussed. Furthermore, validation, testing, optimization potential, etc should be considered.

The aim of the review is to show essential advantages of the method to detect metabolites in humid exhaled air. Further papers should address specific questions of different kinds of lung diseases, effect of bacteria, medication, nutrition, etc.

Experimental details

In the past decades, there was a balance between advances in the understanding of principles of IMS, often leading to new applications, and the design of IMS instruments. IMS has a significantly large information density with comparative low burden in weight, power and size. There are other analytical techniques, which contain much greater information density like mass spectrometry. Other techniques are smaller and more economical on power such as surface acoustic wave sensors. IMS shows its specificity depending on ion size, chemistry and nature of the sample. It can be very high, through a combination of drift time and ionization properties. When it is possible, hyphenated GC-IMS are always preferred. IMS has some practical advantages compared to MS and GC, especially with respect to utilities (weight, size, power consumption), gas consumption, no vacuum is required and relatively low power requirements. Compared to FTIR the IMS has advantages with respect to the minimum detection limit, FTIR shows problems with optical interference and optical windows, particularly in humid air. The disadvantages of most sensor techniques are the high level of cross sensitivity [1].

General principles of operation

The term ion mobility spectrometry refers to the method characterizing analytes in gases by their gas phase ion mobility. Normally, the drift time of ion swarms formed using suitable ionization sources and after passing electrical shutters is measured [106]. Ion mobilities are characteristic of analytes and can provide a means for detecting and identifying vapours. The drift velocity is related to the electric field strength by the mobility. Therefore, the mobility is proportional to the inverse drift time, which will be measured at a fixed drift length.

Ion mobility spectrometry combines both high sensitivity and relatively low technical expenditure with high-speed data acquisition. The time to acquire a single spectrum is in the range of 10 ms to 100 ms. Thus, an IMS is an instrument suitable for process control, but due to occurrence of ion–molecule reactions [26, 107–114] and relatively poor resolution [115–123] of the species formed, it is generally not suitable for the identification of unknown compounds. Compared with mass spectrometry, the mean free path of the ions is much smaller as the dimensions of the instrument. An ion formed has a high number of collisions with carrier gas molecules on the drift way towards the Faraday plate. However, because of the high vacuum conditions in mass spectrometry, an ion formed there will normally have no collision with other molecules during the drift. Thus, ions within an IMS are collision stabilized. In the small time gap between the collisions, the ion will gain energy from the external electric field and lose the energy by the next collision process. Consequently, a rather constant drift velocity will be reached quickly. Therefore, an ion swarm drifting under such conditions experiences a separation process that is based on different drift velocities of ions with different masses or geometrical structures [124–128]. Collection of these ions on a Faraday plate [129, 130] delivers a time-dependent signal corresponding to the mobility of the arriving ions. Such an ion mobility spectrum contains information on the nature of the different compounds present in the sample gas.

The most important parts of the instrument are the three regions for ionization, reaction and drifting (see figure 1). The external and homogenous electric field will be established within the drift tube using several drift rings for stabilization. The carrier gas will take sample molecules within the ionization region when the shutter is open. The ionization of the analytes occurs by chemical ionization on collisions of the analyte with ionized carrier gas molecules by application of radioactive ionization sources. A so-called drift gas [131–135] will flow from the Faraday plate towards the ionization region (not shown in figure 1.). Normally, if the

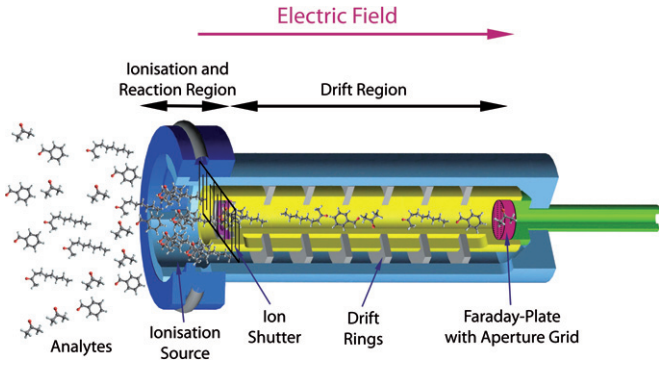

Figure 1. Working principle of an ion mobility spectrometer (IMS).

shutter is closed, no ions could reach the drift region. In addition, a so-called drift gas directed contrary to the drift of ions will protect the drift region. Thus, in an ideal case, no neutral analyte molecules should enter the drift region. If the shutter is held closed, all analyte molecules, neutrals and ions will be washed out on the gas outlet. During the shutter opening time, some ions will enter the drift region. During several collisions with the surrounding gas molecules, a steady drift velocity will be reached. In the ideal case, if no other chemical reactions, clustering, etc occur, totally separated ion species will reach the Faraday plate. The time-dependent voltage or current measured during a time interval from half of the shutter opening pulse is called the ion mobility spectrum. Using air as carrier gas, normally the carrier gas molecules are ionized by the β-particles directly. In the present case positive ions are under consideration. These primary positive ions of the carrier gas (called reaction or reactant ions) will undergo different chemical reactions with the analyte ions to form so-called product ions by proton transfer, nucleophilic attachment, hydride abstraction and other pathways. Also charge transfer and proton abstraction could occur. All parts of the IMS, which are in contact with the analytes, were constructed from inert materials.

To realize an effective pre-separation of the rather complex mixtures occurring in exhaled air, a 17 cm long weak polar multi-capillary column (MCC, Sibertech, LTD, Novosibirsk, Russia) made by combining approximately 1000 capillaries (see figure 2) with an inner diameter of 40 μm and a film thickness of 0.2 μm was coupled to the ^{63}Ni-IMS. The total column diameter of 3 mm allows operation with a carrier gas flow up to 150 mL min^{-1}, which is the optimum flow rate for IMS. In addition, the effective separation of humidity is one major advantage of the MCC used, as discussed later in more detail [28, 29, 79, 82, 119, 136–146]. Different stationary phases are available for such columns too; for general purposes mostly the OV-5 phase is applied.

The heating of the column is indispensable for the reproducibility of the chromatographic results. To achieve comparable retention times, the MCC was held at 30 °C (sometimes also 40 °C or 80 °C are applied, but such effects will not be considered here in more detail) during the breath analysis procedure. To realize an isothermal separation, a simple heating construction is needed, which means a concise size decline of the instrument.

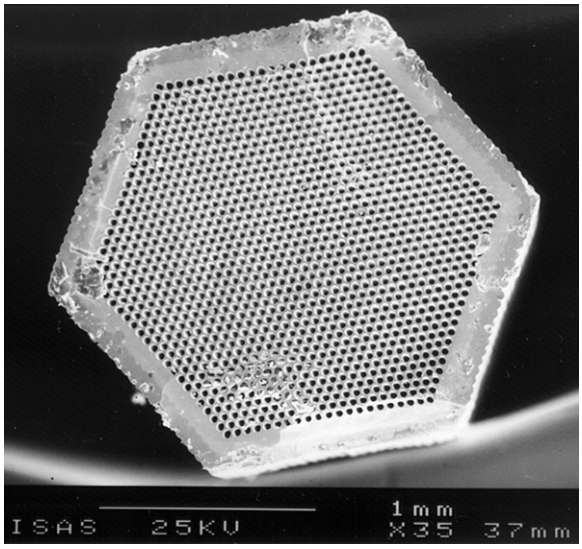

Figure 2. Photograph of a multi-capillary column (MCC), lateral cut.

In the sampling process, a proband blows through a mouthpiece coupled, for example, with a brass/Teflon adapter designed at ISAS into a Teflon tube (1/4″, Bohlender GmbH, Lauda, Germany), which is connected to a 10 mL stainless steel sample loop of an electric six-port valve (Nalco, Macherey-Nagel, Düren, Germany). By switching the six-port valve breath is transported by the carrier gas from the sample loop into the MCC. After passing the column, the separated substances can be directly analysed by IMS. Therefore, the results can be achieved within at the most 10 min depending on the separation time of the compounds. This construction enables a direct and rapid sampling at a known breath volume. The photograph of the instrumentation at breath sampling into the 10 mL loop using the MCC-^{63}Ni-IMS is shown in figure 3.

Application of MCC/IMS for humid air

The kind of ions will differ depending on the ionization method [1, 6]. The most frequently used ionization techniques are radioactive sources (alpha and beta radiation [1, 4]), UV lamps [147–150] (ionization energies between 8.6 eV and 11.7 eV, normally used are 10.6 eV lamps [121, 138, 144, 147, 151–154]), lasers [9, 12, 155–162], electrical discharges (e.g. corona [163–172] or partial discharges [173–175]) and electrospray [12, 44, 176–185]. UV lamps will not be applied for humid air, because of the limitation in the transmission of the UV light through LiF or Mg_2F-windows, which are hydroscopic. Discharges will form much more ions because of the destruction process [174, 176, 186–190] and are not used up to now for applications in the field of breath analysis.

Generally, nitrogen or air is used as a carrier gas; the carrier gas molecules are ionized by the β-particles directly. Positive carrier gas ions and free electrons will become available. These primary positive ions (called reaction ions) will undergo different chemical reactions with the analyte ions to form product ions by proton transfer [112, 191–194],

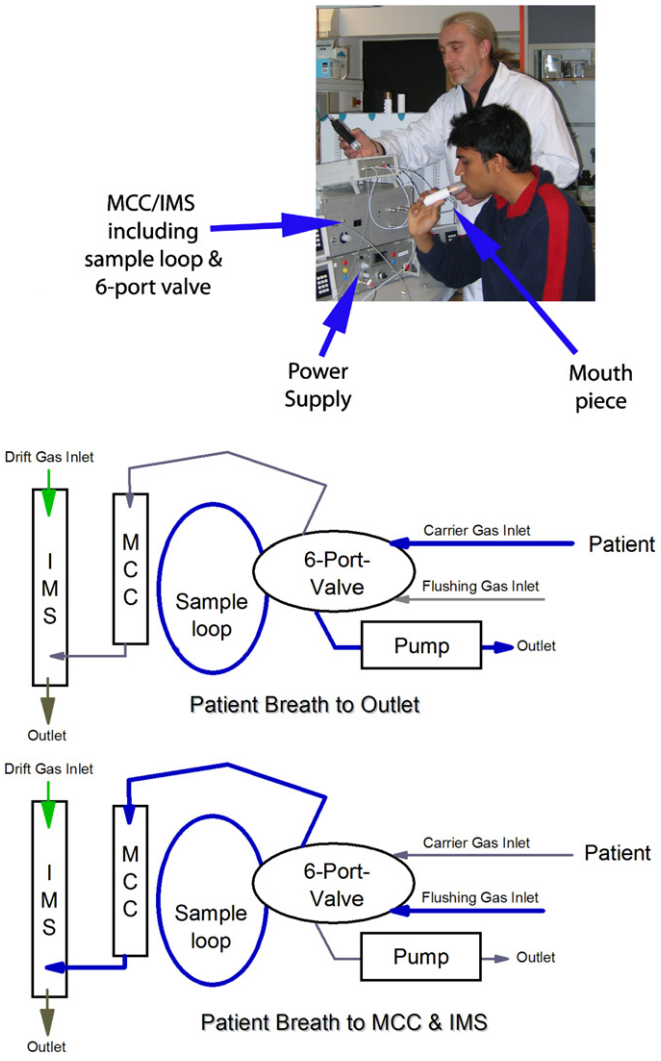

Figure 3. Sampling procedure of human breath directly using a mouth piece (above), gas flow plan (below): patient breath through sample loop to outlet and sample loop to MCC/IMS.

nucleophilic attachment [195–197], hydride abstraction and other pathways [1, 6, 198–200]. Nearly thermal electrons would be attached to sample molecules and form negative ions in different ways (electrophilic attachment, resonant attachment, dissociative attachment) [201–205]. Charge transfer [119, 136, 138, 192, 206–208] and proton abstraction [208–212] could also occur. Often, both positive and negative ions are formed. Limitations will come by the total number of ions available, which is realized by the reaction ion peak. By chemical ionization, the total number of ions formed from the analytes could not be higher than the number of ions providing the reaction ion peak. Furthermore, monomer and, with increasing concentration of the analyte, dimer ions will be formed [1, 6, 198–200].

With respect to the application of MCC/IMS for analytes in air, the major ionization processes should be considered. Electrons emitted from the ^{63}Ni foil collide with atoms or molecules of the carrier gas. If nitrogen is used as drift gas, the released energy amounts to 35 eV per collision. Nitrogen is ionized as long as the energy of the radiation is higher than its ionization potential of 15.58 eV (equation (1)). This starting reaction which can also be observed in air initiates further competing reactions [4]:

$$N_2 + \beta^- \rightarrow N_2^+ + e^- + \beta^{-*} \quad (1)$$

$$N_2^+ + 2N_2 \rightarrow N_4^+ + N_2 \quad (2)$$

$$N_4^+ + H_2O \rightarrow H_2O^+ + 2\,N_2 \quad (3)$$

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH \quad (4)$$

$$H_3O^+ + H_2O + N_2 \rightarrow (H_2O)_2H^+ + N_2 \quad (5)$$

$$(H_2O)_2H^+ + H_2O + N_2 \rightarrow (H_2O)_3H^+ + N_2. \quad (6)$$

The formation of positively charged water [193, 213–216] clusters of the type $(H_2O)_nH^+$ as described by reactions (1)–(6) was proved by 'high-pressure' MS investigations. The number n of water molecules contained in the cluster depends on the temperature and water content. At a temperature of 25 °C, a pressure of 700 Torr and a relative humidity of 20%, the clusters contain five to eight water molecules [1, 199, 200]. Different IMS/MS investigations indicate that the peak formed by the reactant ions is not only formed by the water clusters described above. As recorded IMS/MS spectra clearly show, the clusters contain, besides water, nitrogen or other drift gas components [1, 6, 10, 199, 200, 217].

Considering the formation of negatively charged ions, sample molecules are ionized by the attachment of electrons in the case nitrogen is used as a carrier gas. If air is used as a carrier or drift gas, O_2^- ions as reactive species are dominant. In humid air, attachment of water can be observed. The formed ions have the composition $(H_2O)_nO_2^-$. Additionally, ions with the composition $(H_2O)OH^-$ and O_4^-, CO_4^-, CNO^-, Cl^- and CN^-, partly also in hydrated form, were detected [4]. Therefore, depending on the polarity of the external electric field within the drift region, positive and negative ions could be investigated.

The formation of positively charged product ions depends on the proton affinity of the substance to be ionized. Since the proton affinity of water is very low, the water clusters described above ionize a great number of organic compound classes [193, 194].

The reactions dominating the ionization process to form positive product ions from the analyte molecules AB are summarized in equations (7)–(9), to form negative ions, as shown in equations (10)–(12):

$$(H_2O)_nH^+ + AB \rightarrow (AB)H^+ + nH_2O \quad (7)$$

$$(H_2O)_nH^+ + AB \rightarrow (AB)(H_2O)_mH^+ + n - mH_2O \quad (8)$$

$$(AB)(H_2O)_mH^+ + AB \rightarrow (AB)_2H^+ + mH_2O, \quad (9)$$

whereas for low concentrations, only equations (7) and (8) apply; in the case of higher concentrations the formation of dimer product ions according to equation (9) is observed [1, 6, 199, 200].

The reactions taking place in the case of negative product ion formation are closely related to the ionization processes observed in an electron capture detector (ECD) used in gas chromatography [1, 4, 198, 200, 217]:

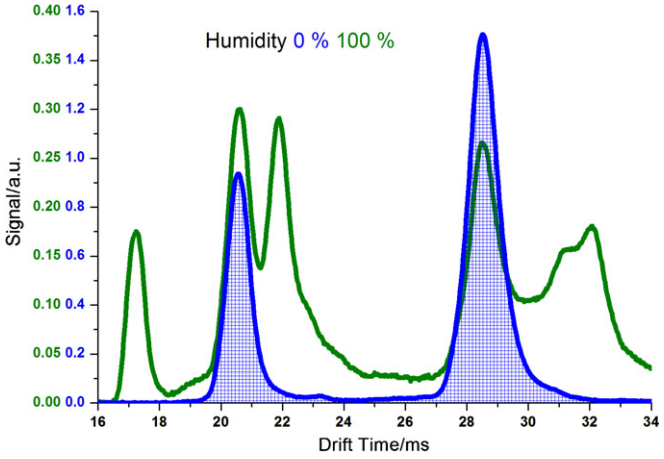

Figure 4. Direct detection of alpha-pinene by IMS (without a GC column) at 0% humidity (two peaks) and 100% humidity (showing additional peaks).

$$[(H_2O)_3O_2]^- + AB \rightarrow [AB]^- + 3H_2O + O_2 \quad (10)$$

$$[(H_2O)_3O_2]^- + AB \rightarrow [(AB)O_2]^- + 3H_2O \quad (11)$$

$$[(H_2O)_3O_2]^- + AB \rightarrow A^- + B + O_2 + 3H_2O. \quad (12)$$

Halogenated hydrocarbons are subject to a dissociative charge transfer reaction analogous to equation (12). At high analyte concentrations, this reaction leads to the formation of adducts. Analogously, the formation of O_2^- adducts is observed. Reactions strongly depend on the analyte concentration, temperature and on the humidity of the measuring tube. Equations (13)–(15) summarize reactions of halogenated compounds with strong dependences on the concentration of the analytes [1, 4, 198, 200, 217]:

$$(AB - X) + O_{2^-} \rightarrow X^- + AB + O_2 \quad (13)$$

$$(AB - X) + O_{2^-} \rightarrow (AB - X)O_2^- \quad (14)$$

$$(AB - X) + X^- \rightarrow (AB - X)X^-. \quad (15)$$

Because of the minimum detection limit down to the pg L^{-1} range it should be noted that IMS is susceptible to impurities in the carrier gas or common ambient pollutants in air monitoring [1, 4, 198, 200, 217].

To describe the quantitative aspects of ionization, the following main processes should be considered:

- primary ionization (formation of reactant ions, direct ionization by UV light),
- ion–molecule reactions and other processes necessary for the formation of product ions,
- recombination processes of positive and negative ions,
- diffusion of ions towards the walls of the drift tube and
- loss of ions due to the drift gas.

Resolution

Unfortunately, the resolution [116, 117] of an IMS is often insufficient, the peaks overlap or interactions between different ions occur. Therefore, it is often necessary to pre-separate

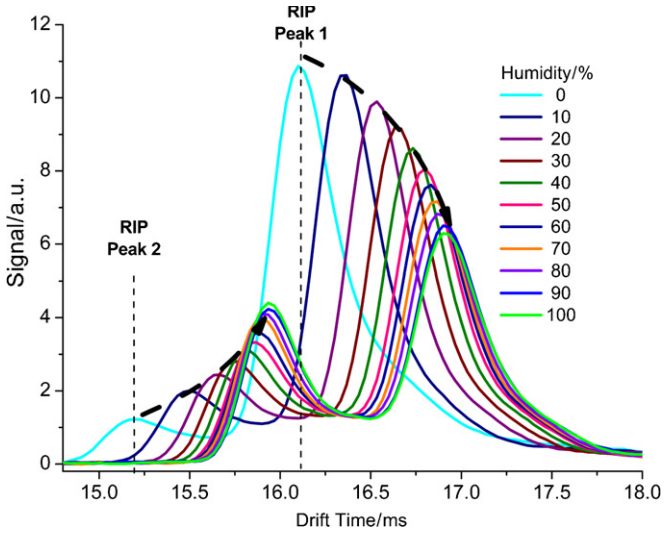

Figure 5. Influence of humidity on the spectra at different levels of humidity: RIP, reactant ion peak; peak 1, $(H_2O)_nH^+$; peak 2, $NH_4^+(H_2O)_n$.

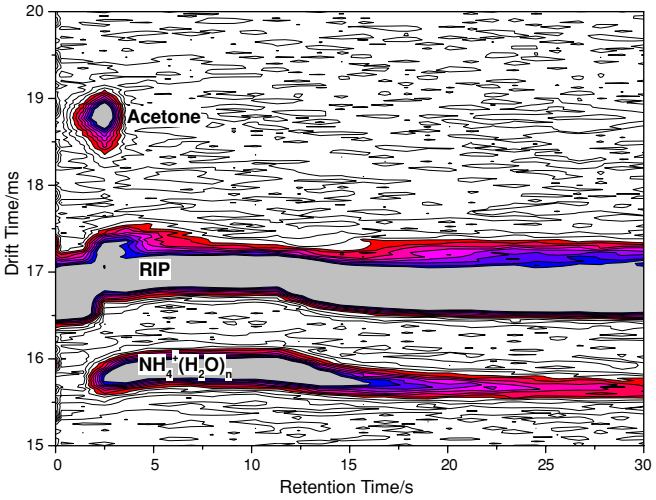

Figure 6. Separation of humidity and analyte acetone within an IMS chromatogram.

the substances before entering the IMS. Thus, in addition to the registration of the total ion current which is generated by ionization of the eluted compounds, selective detection is achievable by the acquisition of complete ion mobility spectra at all retention times. Some different interfaces for the GC/IMS coupling are introduced where both packed columns and capillary columns are used. Problems arising from column bleeding and the long dwell times of molecules in the reaction region result in undesirable reactions. Improvements were reached by using multi-capillary columns, which were originally developed at the present Institute for Applied Physics and the Institute of Catalysis in Novosibirsk, Russia. Measurements made earlier to characterize these columns show that the number of theoretical plates per column was high enough (5000 per metre) to merit further evaluation. The size of these columns, up to 30 cm for rod-shaped columns and up to 100 cm for spiral columns and 3 mm in bundle diameter

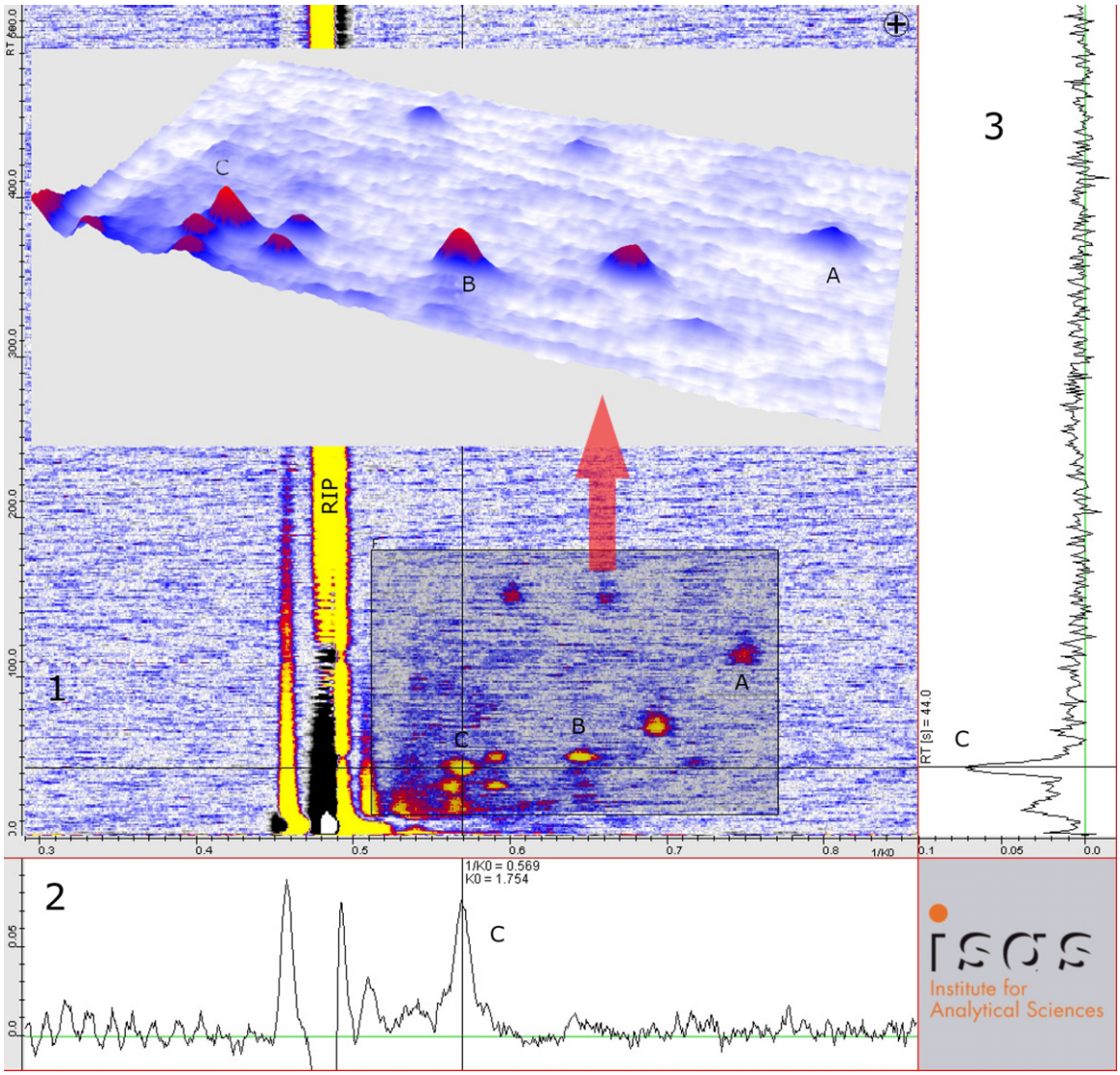

Figure 7. Typical IMS chromatogram of a sample of human breath. Window 1: IMS chromatogram (x-axis: $1/K_0$ (V s cm^{-2}); y-axis: retention time (s)). Window 2: single spectrum (x-axis $1/K_0$ (V s cm^{-2})). Window 3: height line at the $1/K_0$ value of peak C (y-axis: retention time (s)). Inset: 3D plot of the detail area marked in the IMS chromatogram; peaks A, B and C are mentioned for comparison purposes.

with potential high volumetric flows, are attractive for portable instruments that perform best at elevated flow rates, such as necessary for IMS operation.

Application of MCC/IMS for breath analysis

The influence of humidity on the response of an IMS should be shown exemplarily using the analyte alpha-pinene. In figure 4 single spectra as obtained using an IMS without any pre-separation unit at 0% and at 100% humidity are shown. It comes out clearly that the number of ions formed at 100% humidity is increased compared to humid free air. Thus, for rather humid breath samples, the effect of the humidity must be considered carefully. Therefore, a full variety of ions may be interesting for the characterization of ion–molecule reactions but cause a large number of problems considering the interpretation of spectra.

On the other hand, removing the humidity from a breath sample will result in the reduction of a wide range of organic compounds as the washing out effect. Thus, drying the human breath will not help to overcome the problem. Therefore, a detailed view into the inter-dependences must be realized.

Figure 5 shows the spectra obtained using an IMS without any sample molecules in steps of 10% and relative humidity from near 0% to 100%. In that case, two different peaks, a smaller in front and a larger—both named the reactant ion peak (RIP)—become visible at all values of the humidity shown.

The shift of the relative positions of both RIP becomes clear and the dependences of the position of the peaks RIP 1, such as $(H_2O)_nH^+$, and RIP 2, such as $NH_4^+(H_2O)_n$, will be affected largely (for details of the nature of the RIP ions, see [1, 4, 6, 199]). Therefore, a single view of the mobility values alone will not allow the identification of analytes correctly.

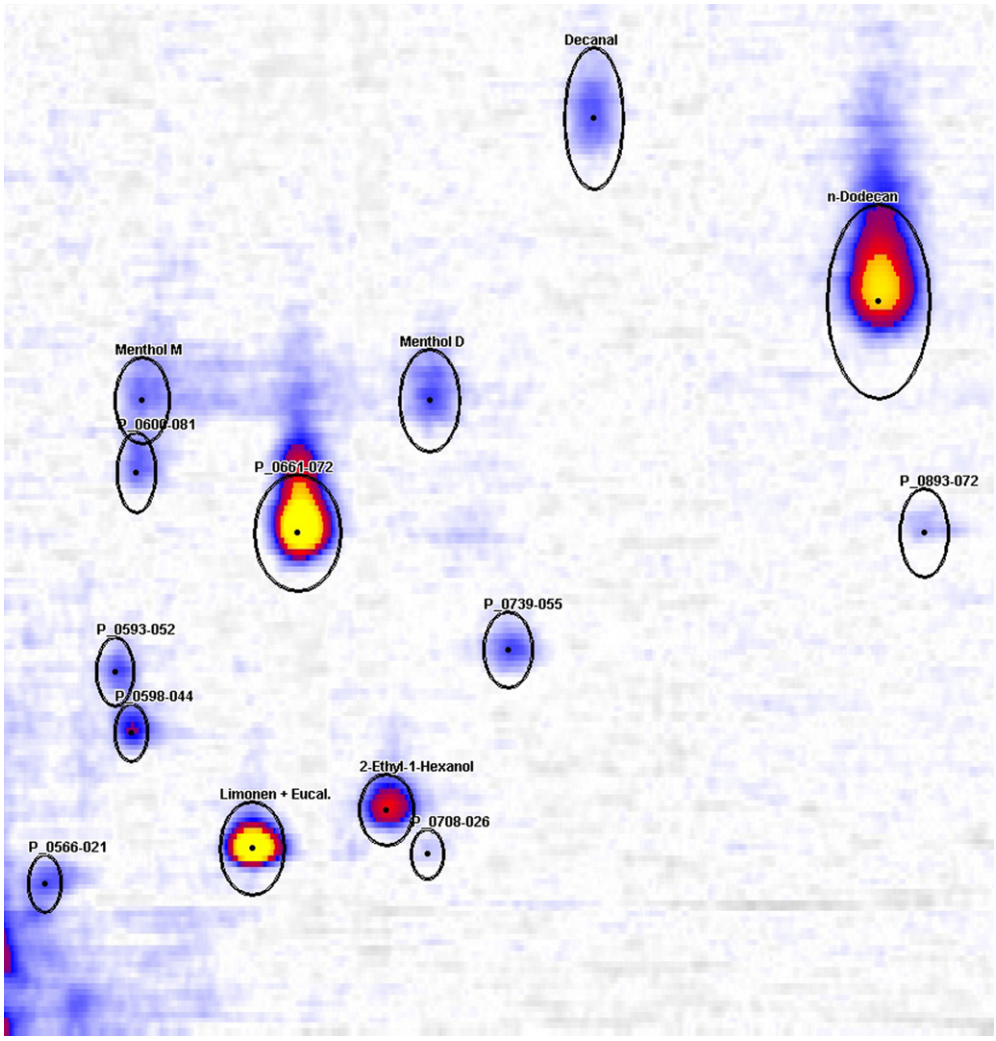

Figure 8. Part of an IMS chromatogram showing automatic peak finding by black circles, and numbering and naming in some cases like limonene in the upper part.

Consequently, a suitable separation of humidity and the analytes in human breath samples is important. Such an effective separation could be realized using a MCC as shown in figure 6. Here, the detection of acetone in air is shown as an IMS chromatogram. The acetone peak is separated clearly from both of the RIPs. It is also visible that the signal marked RIP peak 2 in figure 5 will occur only in a limited interval of retention time. The peak RIP 1—henceforth normally mentioned as RIP only—will occur at all retention times. It is also visible in figure 6 that at retention times between 2 s and about 15 s, a small shift towards higher drift times occurs. Thus, the 10 mL of human breath from a sample loop becomes investigable for all retention times as to be shown later. Only between the retention times 2 s and 15 s and the full drift timescale must the RIP position be considered carefully, if necessary.

A typical IMS chromatogram as obtained by MCC-IMS investigations is shown in figure 7. There are three major windows, indicated as window 1 for the IMS chromatogram, as window 2 for the single spectrum occurring at the horizontal line in window 1 at peak C and as window 3 showing the so-called height line at the $1/K_0$ value of peak C (vertical line in window 1). The inset of figure 7 shows a 3D plot of the detail area marked in the IMS chromatogram of window 1; peaks A, B and C are marked for comparison purposes. The position of the RIP is also indicated in window 1.

On the other hand, figure 7 shows clearly that the RIP will occur over the full retention time axis of 500 s. Thus, a rather continuous water content through the MCC will deliver a RIP at rather constant drift time, besides the comparatively small [2 s, 15 s] region. Thus, the MCC will not only support a rather good separation of different analytes in acceptable time intervals, but it will also provide a continuous reservoir of water molecules. Thus, the full content of water molecules within the sample loop of 10 mL will be spread over 500 s at 30 °C in the case of figure 7.

The raw IMS data were first treated by a baseline correction so that intensity values varied around zero in areas of pure noise. Then the time axes were transformed to adjust for different instrumental and environmental factors, such as length of the drift tube or ambient pressure. Next, the single measurements were subjected to a peak localization procedure [218–220].

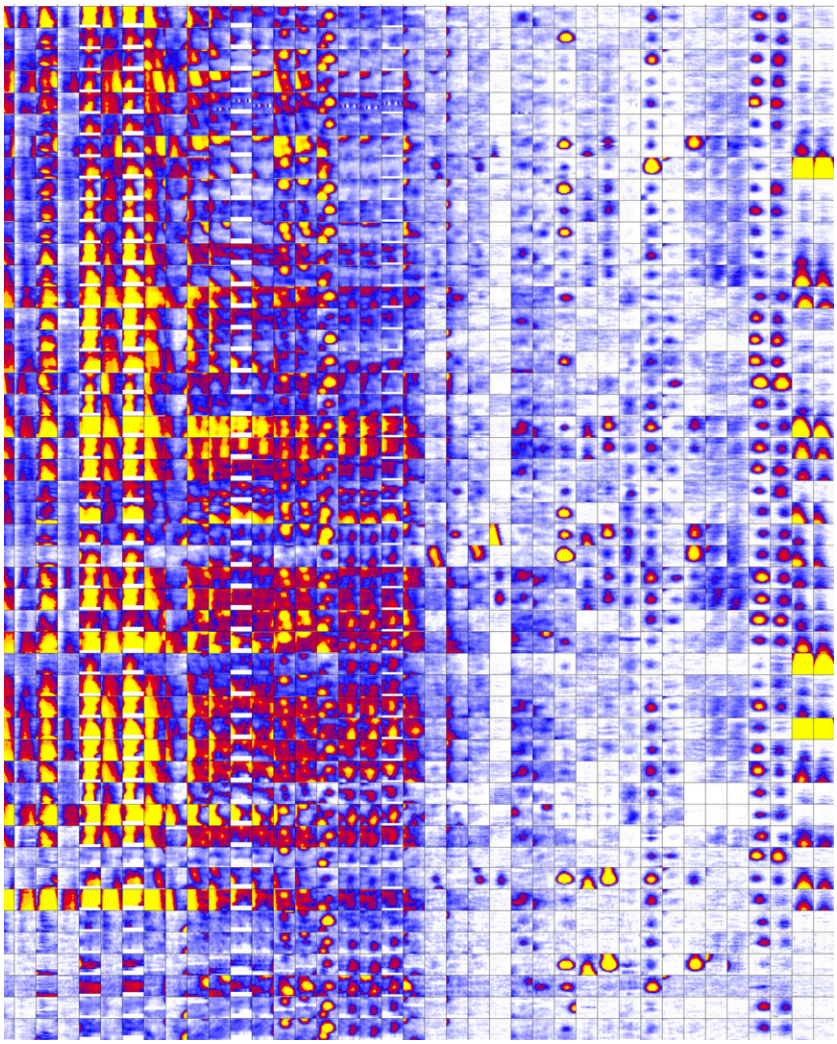

Figure 9. Peaks selected from IMS chromatograms of breath samples of different patients (by comparison of districts within the IMS chromatogram): each line is a patient, each row a specific peak/analyte.

As an example of automatic peak finding procedures which allow location of peaks within specific districts formed by an interval in the drift time and the retention time of the IMS chromatogram in figure 8, the result of such a procedure will be shown, without keeping axis names, only to show the result. There, some analytes are named as limonene, some others are still unknown and have to be named, e.g. by comparison to results of parallel GC/MS investigations on the same breath sample.

With such an automated procedure 'breathograms' of different patients become comparable more or less automatically. A result is shown in figure 8, but details will be discussed in a following paper considering specific cases. Figure 9 shows a selection of peaks selected from IMS chromatograms of breath samples of different patients by comparison of districts within the IMS chromatogram: each line is a patient and each row is a specific peak. The relation of such peaks to specific diseases, airway infections or bacterial colonization is considered elsewhere. The aim of the review is to summarize the potential of MCC/IMS as one method to investigate human breath.

Applicability of the method

In a recent pilot study (following IRB approval from the institution), breath analysis with IMS was performed in healthy employees of the ISAS (Institute for Analytical Sciences) and in voluntary patients of the Hemer Lung Hospital who had a cytological or histological diagnosis of lung cancer. In this pilot study, which was designed to generate preliminary data and a training set of VOC profiles, no distinctions, e.g. regarding smoking history or COPD, were made. Furthermore, patients with lung cancer were not differentiated by stage or histological type of tumour. All participants had given their written informed consent for participation in this study. The study participants were asked to exhale through a mouthpiece connected to a Teflon bulb. Exhaled breath passed through an unheated sampling loop. A miniaturized suction pump was used to realize a homogeneous breath sample flow. At the end of exhalation, thus providing a mainly alveolar sample, an electric six-way valve was switched and 10 mL of gas in the sample loop was directed to the MCC for chromatographic separation of breath compounds.

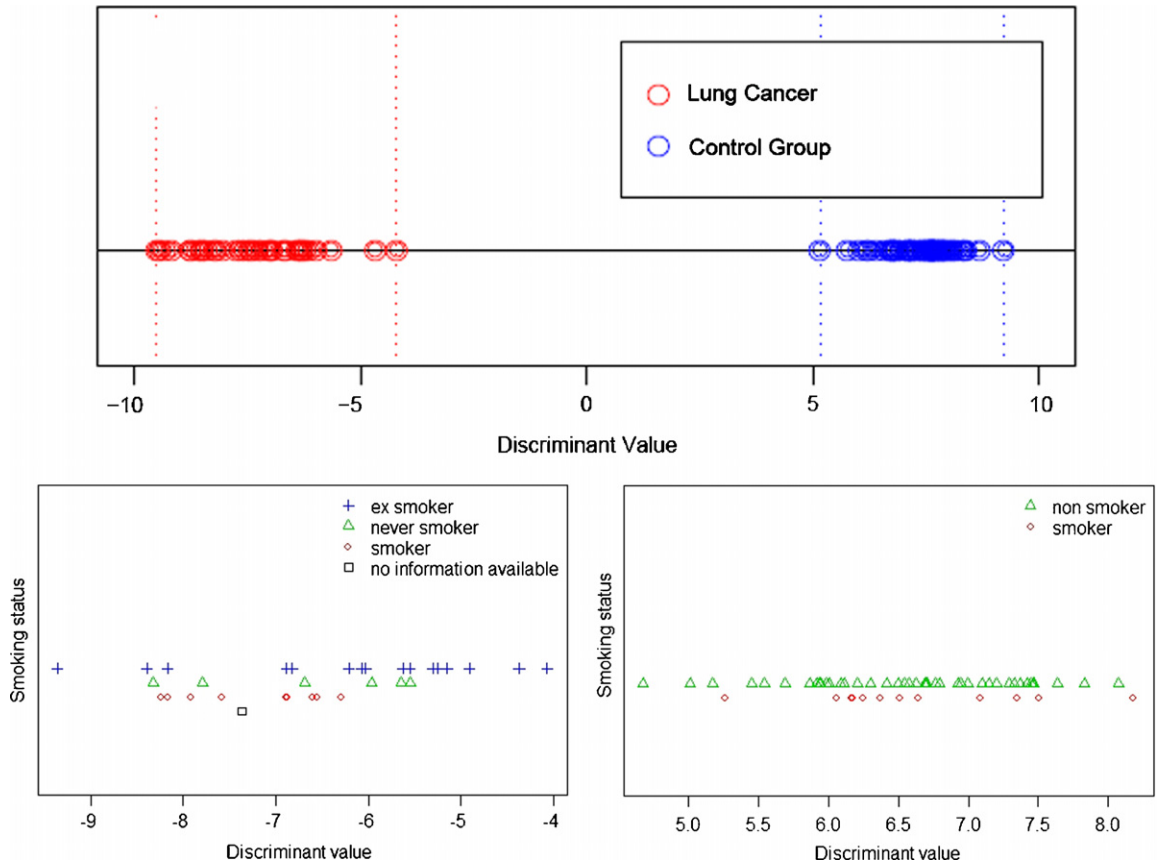

Figure 10. Result of linear discriminant analysis (above) and influence of the smoker status on the discriminant values (below, left bronchial carcinoma, right control group).

Case study

Altogether, 32 patients (24 men, 8 women) with histological proven lung cancer were studied before the initiation of therapy. Mean age was 65.1 ± 9.6 years, body weight 74.9 ± 13.7 kg and height 169.4 ± 8.3 cm. Seven patients had a small-cell lung carcinoma (SCLC); 24 patients had a non-small-cell lung carcinoma (NSCLC), including 1 patient with a carcinoma *in situ*; 1 patient had a mixed tumour with NSCLC and SCLC; and 5 patients had an undifferentiated carcinoma. The tumour stage ranged from Tis to T4N3M1 (stage 0: 1 patient, stage 2: 3 patients, stage 3: 9 patients, stage 4: 17 patients). Seventeen patients were ex-smokers, six patients had never smoked and seven patients still smoked. Fifty-four healthy persons (39 men, 15 women; 12 smokers, 42 nonsmokers) without cancer served as controls. Mean age was 46 ± 12 years, body weight 81 ± 16 kg and height 181 ± 9 cm.

By applying the peak pattern analysis [14, 218–222] as described, a set of 23 variables was differentially expressed between the classes to a multiple test level of 0.001%. Based on these variables, a linear discriminant analysis was conducted. By applying the leave-one-out method to 32 patients and 54 healthy controls, all patients with lung cancer, including the patient with carcinoma *in situ*, and all healthy persons were classified correctly. This yielded a 100% negative and positive predictive value, respectively [223]. The error rate estimated by the leave-one-out method was 0. The separation of both groups was independent of the smoking status. In the lung cancer and the control groups, nonsmokers as well as smokers were present. No clustering occurred on the discriminant value scale for smokers or nonsmokers, neither in the left part related to lung cancer nor in the right part related to the control group. For further details see [76].

The study has certain limitations to overcome in future, but is independent of the applicability of IMS. It should be mentioned to understand the example. Thus, in the study, we included and compared lung cancer patients with healthy controls, but did not address a further prospective classification of lung cancer patients and healthy controls based on the pre-selected combination of VOCs. This difference in the study design may explain the higher accuracy compared to former studies on breath analysis. The lung cancer patients were not matched to patients without lung cancer, and we did not include a further control group with other lung diseases. So the discriminating cluster of VOCs is not necessarily a tumour-specific one. Furthermore, most of the patients had an advanced tumour stage. Further studies are necessary for the discrimination of different kinds of lung diseases and different stages of lung cancer. These studies need blinding with respect to diagnosis to minimize bias. Finally, proper selection of the control group and the classification of subgroups (smoking status, COPD, medication) are necessary.

However, the pilot study was primarily focused on the possibility and the advantages of ion mobility spectrometry as an analytical method. The intention was to show that IMS, as

a new method in breath analysis, can produce discriminating patterns of VOCs. These positive results could not be expected in advance. Data acquisition times of only 10 min offer good pre-conditions for the clinical use of IMS in breath analysis, especially if future computerized peak distribution analysis facilitates and accelerates further evaluation.

Generally, figure 10 shows the separation of the lung cancer group and a healthy control group. As shown in the lower part, no dependences on the smoker status are found on the discriminant values. For a reliable diagnosis and separation of lung cancer from other disorders, further measurements and an evaluation of the discriminating pattern in a larger group of patients are necessary.

Summary

It should be shown that ion mobility spectrometry is a useful method to detect analytes in humid air and is applicable for breath analysis. The formation of positive or negative ions depends on different ionization processes occurring. To reach sufficient separation, pre-separation of the analytes should be considered. Generally, a direct measurement using about 10 mL of human breath and a total analysis time of about 10 min will make IMS applicable for clinical trials.

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