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# Zeptoampere electric current measurements with molecular tagging

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ABSTRACT

A novel method of measuring concentrations of ionized molecules in gases that enables detection of individual ionized molecules by means of tagging them with readily detectable nano-objects has been recently discovered and developed. The femtoampere detection level of this method has been demonstrated. Here we confirm that this detection level is caused by cosmic rays and suggest ways to reduce it. The method was shown to be able to detect 1 ion in $10^4$ $cm^3$ of air in an underground laboratory where the cosmic rays level is negligible. This is an extremely low electric current down to zeptoampere level (1 zA = $10^{-21}$ A). This concept opens doors for advances in detection sensitivity in chemistry, biology, medicine and physics. For example for mass spectrometry this method may increase sensitivity of the absolute current detection (for Faraday collector detectors) by two to three orders of magnitude.

## 1. Introduction

Ultra-low electric current measurements are widely used in science and industry for quantification of trace compounds. For example, in atmospheric science, very low concentrations of ions and molecules determine nanoparticle formation by creating stable nuclei and may affect climate change [1,2]. Another area of application of trace level detection is clean room monitoring.

Detection of an ultra-low concentration of molecules has become vitally important for security applications to identify explosives and illicit drugs in airports and other ports of entry [3]. Often separation methods are based on difference in mobility of ions in electric field. One of such method - Ion Mobility Spectrometry (IMS) - is widely employed as a detection method for explosives in the airports [4].

In medical applications and life science the measurement of Volatile Organic Compound (VOC) biomarkers as diagnostics of cancer and infectious diseases is a rapidly growing area of metabolomics that promises to bring a non-invasive fast diagnostic to points of care [5,6]. An increase in sensitivity will enable diagnosis of earlier stages of diseases and increase patient survival rate. A single cancer cell can generate in the region of circa $10^3$ biomarker molecules in the headspace of several $cm^3$ volume [7,8]. This level of concentration is desirable for detection in many applications, e.g. for single cell or bacteria observations and drug development, but it is not achievable with existing technologies. Concentrations of ions and molecules in these cases are very small - often below parts per trillion (ppt) level.

Currently gas chromatography (GC) and mass spectrometry (MS) based techniques are used to identify and quantify trace levels of molecules in the air, e.g. [9]. IMS and MS detect ionized molecules. Most GC detectors, for example electron captured detector also require ionization of analyte or using electric current amplification circuits as, for example, in thermal conductivity detectors to detect low concentrations. Therefore, quantification of ion concentrations is the most essential element in modern measurements of trace compounds in gases.

Ion concentrations in gases are measured as an electric current by a Faraday cup method. Modern techniques like IMS are close to their physical detection limits due to the thermal fluctuations in the electron gas of metals making measurements below 10 femtoampere over less than 1 s challenging [10]. In some mass spectrometers Faraday detectors are used for absolute current detection and the thermal fluctuations also cause a high background noise. Some mass spectrometers employ charge multiplication, e.g. electron multipliers that enable single ion detection in high vacuum. However, the single ion mode is not a universal solution for MS. In many applications Faraday collectors are used, e.g. detection in air samples of illicit drugs at very low level or measuring isotope ratios.

Sensitivity of MS is also affected by losses in the air-vacuum interface when a sample of air with an analyte is transferred from the air pressure to the high vacuum necessary for ion separation. In practice, because of these losses in the air-vacuum sample transfer it is extremely challenging to measure concentrations below the ppt level of analyte in the air sample (circa $10^{11}$ molecules per $cm^3$). Thus, electric currents measured with Faraday cup detectors are in the high femtoampere level. This restricts progress in trace concentration measurements in many areas.

A fundamentally novel concept of quantifying the concentration of ionized molecules in gases that enables detection of individual ionized molecules by means of tagging them with readily detectable electrically

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neutral nano-objects (hereafter Nanotechnology Molecular Tagging (NMT)) has been recently discovered [11]. It was found that this method can provide a breakthrough in sensitivity by enabling a single ion or electron to be detected in an air sample of large volume. This potentially provides an increase in sensitivity by several orders of magnitude in comparison to existing methods. In this paper the low detection limit of an NMT device was investigated by measuring background noise level of ion counts in an environment where ionizing radiation is negligible – in the Boulby Underground laboratory.

## 2. The NMT and the background noise

In the previous paper, an average background count rate for an NMT device in a laboratory at the ground level was found to be 5 count per $cm^{-3}$ and assumed to be caused mainly by cosmic rays [11]. It is important to test this assumption directly in an environment where the cosmic rays are considerably reduced because there are other sources of ionizing radiation of terrestrial origin, e.g. associated with the natural Radon cycle. Minute traces of radioactive substances for example $^{60}Co$ are found in some engineering materials including stainless steel. Potentially all sources of ionizing radiation terrestrial and cosmic origin can be responsible for the background counts in the NMT. The background counts determine the detection limit. Thus, identification of the origin of the background may help to find how to reduce it and, therefore, increase sensitivity of the NMT.

The NMT background count level without ionizing radiation is expected to be determined by the zero count level of the Optical Particle Counter (OPC). The zero count level for OPC used in NMT was measured to be $< 1$ in $10^5$ $cm^3$. This shows that reducing ionizing radiation may decrease the background counts considerably.

## 3. Experimental

Several ion counter versions according to the concept described have been built. Each version of NMT contains 4 modules: a tag generator, a tagging chamber, a tagged ion extraction chamber and an OPC [11]. In the first module (the tag generator) spherical particles are formed by binary homogeneous nucleation [12,13]. Several semi volatile liquids were used, e.g. dimethyl phthalate and glycerol-water solutions. The generator comprises a stainless steel cylinder condenser and a tube saturator [14]. The modal size of tag particles was from Rt = 100 nm to 300 nm. The particle number concentration was in the range from $1{\cdot}10^6$ $cm^{-3}$ to $6{\cdot}10^7$ $cm^{-3}$.

The second module (the tagging chamber) has a cylinder chamber of 20 $cm^3$ volume inside a stainless steel block with two inlets and an outlet. A sample flow (0.2 L/min) containing ions enters the tagging chamber through one inlet and the flow of tags (0.3 L/min) enters the chamber through the other inlet. For this arrangement, the number concentration of tagging objects was much greater than the number of ions and the ion tagging efficiency was from 70% to 98% [11]. The tagging efficiency is mainly influenced by the size of tagging objects and mobility of ions. The efficiency was evaluated by comparing ion concentrations with OPC counts. The mixture of charged tagging objects and neutral unchanged tags was directed to a charged tag extractor through the tagging chamber outlet.

The rectangular charged tag extractor (third module) was built according to [15,16]. The mixture flow inlet (delivering charged and neutral tags) is shown at the bottom of the extractor on the left and a clean air flow above it (Fig. 1). The mixture of charged and neutral tags without an electric field in the gap between the electrode plates moves horizontally in the lower part of the flow to the excess tags outlet. When a sufficient strength electric field is formed between the stainless steel electrodes charged tags (tagged ions) are separated from the rest of the neutral tags and moved into the adjacent clean laminar gas flow that is directed then to an OPC (MetOne, Pacific Scientific Instruments) where the tagged ions are counted in the OPC individually.

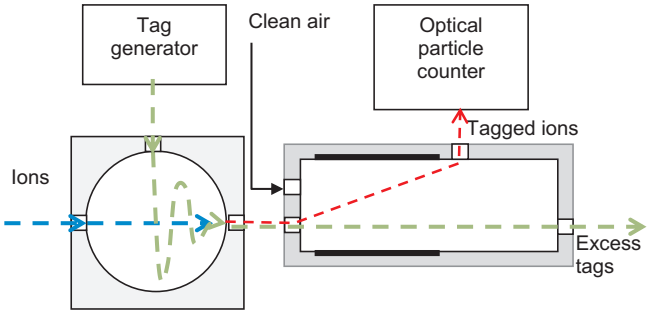


**Fig. 1.** Schematic of the close loop ion counting set-up. The neutral tagging object trajectories are shown with dashed green lines. The probe flask is shown with a thin wall circle. The blue dashed line schematically shows the trajectory of a high energy proton from a cosmic ray. The dashed red line indicates the direction of the tagged ions; two bold horizontal lines show electrodes in the extraction chamber. The rectangle with grains at the top is a tag filter.

## 4. Detection limit of the NMT device measured in the underground laboratory

A device according to the NMT concept is not affected by thermal fluctuations in the electron gas of metal conduits of circuitries. However, there are other potential sources of the ionizing radiation that can generate background noise in NMTs.

Terrestrial ionizing radiation can be reduced or removed by purging Radon and Radon progeny out of internal air conduits with a clean gas. To evaluate effects or cosmic rays a “close loop” NMT set-up was used, Fig. 1.

The term “closed loop” was employed to emphasize that there is no inlet of any gaseous sample from outside into the device. Actually there is neither inlet nor outlet at all. The flow coming out of the OPC was filtered and directed to the tag generator (see the top black line connecting the OPC and the tag generator in Fig. 1). The “Excess tags” flow was filtered with a tag filter (not shown) and introduced into the separation chamber as the “Clean air”. Therefore, all ions counted by NMT were formed by external sources of ionizing radiation penetrating the flask wall.

First the set-up shown in Fig. 1 was tested above ground with the small tagging chamber 20 $cm^3$. The tag flow contains only neutral tags and clean air without ions. In these tests average ion background count number concentrations were 5- counts per $cm^3$. This confirms results obtained previously [11] where a different set-up was used.

These background counts were further investigated above ground using close loop NMT (Fig. 1). The flasks were made from a number of materials: stainless steel, steel, aluminum, Nylon, Polyoxymethylene and glass. It was confirmed that the material of the external flask does not affect the counts. Removal of radon from the air does not affect the number of counts either. The average background counts were strongly influenced by volume of the external flask, Fig. 2a. Therefore, it confirms that the counts observed were associated with ionizing radiation that penetrates flask walls and ionizes air molecules in the external flask and finally tags.

Next an NMT device was tested in the Boulby Underground Laboratory [17]. This laboratory is located at 1100 m below ground in Boulby Mine on the North East coast of England. The environment in the laboratory has an ultra-low background radiation including cosmic ray radiation that is $10^6$ times less than on the surface. The NMT unit with a 1000 $cm^3$ flask was placed in a lead castle built from lead bricks and shielded with 14 mm ultraclean copper sheets, Fig. 3.

The ion count rate in the underground laboratory was practically equal zero. Only few single counts were observed during the tests. It is rather difficult to interpret a single event. For example, a single count at 77 s (Fig. 2b) might be caused by either an extremely high-energy cosmic ray particle or emission caused by minute contamination of the

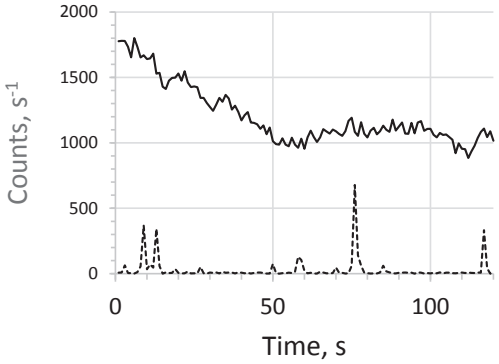


**Fig. 2a.** NMT count rate vs. time for external flask of 20 $cm^3$ (dashed line) and 1000 $cm^3$ (solid line). Measurements were taken in a laboratory above the ground.

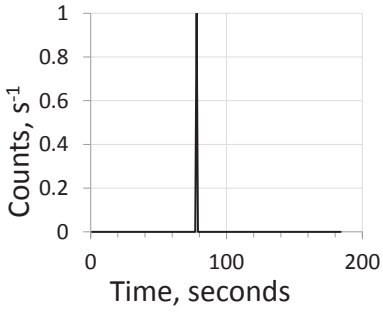


**Fig. 2b.** An example of the NMT count rate vs. time for external flask of 1000 $cm^3$ within the lead castle in the underground laboratory.

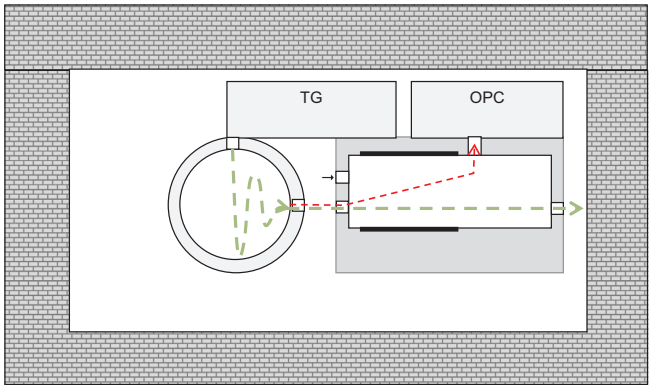


**Fig. 3.** Simplified schematic of the close loop NMT inside the lead castle. The neutral tagging object trajectories are shown with dashed green lines. The flask is shown with a thin-wall circle. The dashed red line indicates the direction of the tagged ions; two bold horizontal lines show electrodes in the extraction chamber. A gray rectangle indicated with TG is the tag generator and a gray rectangle with OPC is the optical particle counter. The clean air inlet to tagged ions extractor is shown with a black horizontal arrow (→). The tag filter is not shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stainless steel flask for example by $^{60}Co$. In addition, this might be caused by malfunctioning of NMT. To confirm that the NMT operated correctly a special test was conducted. The top layer of lead bricks were removed and a very small $^{137}Cs$ conceal radiation source was placed on the copper sheet of the castle. This source instantly generated an avalanche of counts, Fig. 4. This proved that the NMT device was functioning correctly. It also shows possibility of using the NMT with an external probe (flask) to detect radiation and concealed radiation threats (the very small $^{137}Cs$ concealed radiation source was inside a

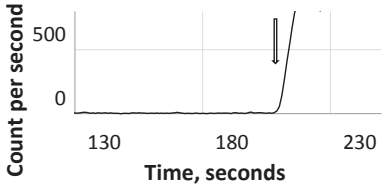


**Fig. 4.** NMT count rate vs. time for probe flask of 1000 $cm^3$ in the lead castle in the Boulby Underground laboratory with a concealed $^{137}Cs$ source placed in the vicinity of the flask at time 210 s marked with an arrow.

lead container).

The NMT count rate at 130 s < time < 210 s was about 10 counts per second, Fig. 4. This count rate was greater than the count rate in Fig. 2b because the top layer of lead bricks was removed allowing traces of radiation in the underground laboratory to penetrate the flask walls.

The observed effect of flask volumes on ion counts show ways to reduce background count rates and the low detection limit of the NMT. They are a) decreasing the tubing ID in NMT air conduits, b) designing tagged ion extraction chambers of a smaller internal volume and c) reducing volume of the tag generator.

It is difficult to evaluate the low detection limit for the NMT technology because of the small number of counts observed in the underground laboratory. The ion count rate of 1 ion per 180 s with flow rate 0.3 L/min gives an estimate of the concentration $10^{-4}$ per $cm^3$. It was assumed that the ion detected in Fig. 2b was caused by an ion in the external flask. It is perhaps the upper limit of the low detection limit for the NMT unit employed.

It is possible to hypothesize that if the external flask is manufactured from materials that have a very low ionizing radiation level the low detection level would be even lower than $10^{-4}$ per $cm^3$. This indicates an extremely low electric current equal to circa 1 elementary charge per 100 s or 1.6 zeptoampere (zA); 1zA = 0.001attoampere or 0.000001 femtoampere. This level of electric current at the atmospheric pressure is very difficult to measure with conventional methods.

There is no reason why the flask volume of $10^4$ $cm^3$ cannot be increased. It is feasible that enlarging the probe will enable the building NMT units with a considerably lower detection limit.

There are other methods that have been used for detection of trace compounds in gases, for example methods based on spectroscopy and photonics. They demonstrate in laboratory conditions relatively high level of sensitivity but use of these methods in practice is very limited either due to contamination issues (humidity and airborne particulate matter) or poor reproducibility [18]. Some methods based on fluorescence are used to increase detection sensitivity. For example, fluorescent molecules used for labelling biomolecules, e.g. proteins in cells. They can provide considerable increase in sensitivity due to their property of repeated light emission upon excitation [19]. It promises very high sensitivity but in practice there are many hurdles associated with bleaching due to high intensity of the incident light, solvent effects and concentration quenching making it challenging to achieve reproducible detection of single molecules in large air sample volumes.

## 5. The NMT and mass spectrometers

GC/MS is the most widely used analytical tool for chemical analysis especially traces organic compounds in the air. It is interesting to see if the NMT can be used to enhance sensitivity of mass spectrometers. There are many applications where absolute current measurements with Faraday collectors are employed in MS. For example, the measurement of precise isotope ratios requires the use of Faraday collectors to reach the necessary precision and accuracy, especially for high dynamic range measurements.

Most mass spectrometers require high vacuum for separation and detection of ions. The NMT device presented in this paper has been

designed for instruments that do not require vacuum. Nevertheless, it is possible to speculate that the main NMT components can be tailored to work in high vacuum as well as at atmospheric pressure. Indeed using low vapor emission materials, the OPC and the charged tag extractor can be easily redesigned for high vacuum conditions. As far as the OPC is concerned it should perform even better in vacuum because of absence of the Relay scattering from gas media. Tag generating in vacuum is the main challenge. In general, homogeneous nucleation is possible in vacuum but it might be necessary to find low volatility tagging material compatible with vacuum conditions. Moving the sample of ions in a vacuum is even easier than in the air because in vacuum there is no Brownian diffusion causing broadening of the ion beam and it is easy to focus ions with electric and magnetic fields. Thus, it is feasible to design an NMT detector for high vacuum mass spectrometers to increase the sensitivity by replacing Faraday plate detectors with the NMT.

Charge multiplier devices are often used in MS to measure low currents. In the single ion mode their detection limits are very low. However, performance of the charge multiplier devices is influenced by the mass of ions. The efficiency of charge multipliers decreases rapidly at high m/z. It might be advantageous to use NMT detectors instead of charge multiplier devices for ions with high m/z.

There are mass spectrometers on the market that work at low pressure, e.g. MX908™. For this type of device, so called high-pressure mass spectrometers, the NMT can replace Faraday plate detectors without redesigning main NMT components. These mass spectrometers are fielded and employed for explosive and contraband detection. The increase in sensitivity by employing the NMT is of great importance for these applications.

## 6. Conclusions

The NMT ion counting technology was shown to be able to detect 1 ion in $10^4\,cm^3$ at atmospheric pressure. Therefore, an incredibly low electric current down to zeptoampere level (1 zA = $10^{-21}$ A) has been measured. The zeptoampere level is the detection limit for the current NMT design but not the detection limit of the NMT method. The NMT can also detect very small radiation contamination levels. The ion counting by tagging may bring the benefit of high sensitivity to many devices used as for security applications like IMS (explosive threat detection at airports) as for general trace chemical analysis applications where GC or MS are widely employed.

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