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Gas-Phase Isotopic Immunometry based on Reflectron-Assisted *in Situ* Detection of Products of Gas Chromatographic Separation of Antibodies and Antigens

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Review Article

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Abstract

The system for gas-phase immunometric measurements with isotopic resolution is proposed. This system based on the reflectron-based Finnigan MAT mass spectrometer can be used in combination with gas chromatograph or gas-liquid chromatographic device. The IMMUNOREFLECTRON-2016 project has been quickly closed for the organizational \ administrative reasons, and all the schemes are now confined in the room where this project has been started. Consequently, it is only possible to propose the variants of similar research and development task solutions in different conditions.

Keywords: Immunometry; Radioimmunology; Gas Chromatography; Gas-Liquid Chromatography; Immunochemistry

Introduction

It is well known that gas chromatography (including gas-liquid chromatography), and particularly, gas chromatography with mass-spectrometric detection, is the classical instrument for antigen / antibody measurements and antibody-assisted experimental immunological investigations. Alternative gas phase detection techniques, such as surface Plasmon resonance spectroscopy on the solid-state antibody-containing carrier or gas-phase electrophoretic molecular mobility analysis are not so useful, because they are very exotic (instrumentally) [1-10]. Despite this fact, the best analytical sensitivity for all chromatographic and precipitation techniques, including gas chromatography, can be realized only in mass-spectrometric detection with isotopic resolution. For example, for accurate or selective measurement of protective antigen in plasma isotope dilution mass spectrometry can be used with preliminary immunocapture or, in different case, precision analysis of some specific antigen isoforms using immunoprecipitation can be realized only in stable isotope labeling mass spectrometry [11,12]. Equivalent resolution is useful for antibody measurements and antibody-assisted investigations. For example, inductively coupled plasma mass spectrometry technique can be used for the quantification of metal-antibody based drugs using stable isotope tracing [13]. Isotopic approaches for antigen or antibody detection are not only good techniques for immunology, but also they are big challenges for labeling mass spectrometry techniques, for example, the production and application of high quality stable isotope labeled monoclonal antibodies is a powerful tool for mass spectrometry analysis using labeled antibodies, which can be used in experiments, approved by ultrahigh-precision standards, such as SISCAPA (Stable-Isotope Standard and Capture by Anti-Peptide Antibody) [14,15]. Unfortunately, they are not useful in GC-MS techniques, because the LC-MS (particularly, HPLC-MS, UPLC-fluorescence-MS etc.) are more applicable in "liquid" biochemistry [16-18]. Many isotope effects, investigable in gas phase, in aerosol conditions or in gas-liquid / solid-gas interfaces are measured in soft matter or liquid conditions [19,20].

Despite this fact, gas chemistry is not inappropriate in immunochemistry and, consequently, such techniques cannot be interpreted as a "Cinderella of contemporary immunology". Many gas effects in immunology have been studied in the past century, starting from the observation of the effect of mustard gas on antibody formation (this

research trend has been stable before the second part of 1960th) and continued in the last decade of the last century by the gas-phase assisted antibody production investigations [21-25]. "Gas phase immunology" (*sensu lato*) is a potentially fruitful research area, which started from the immunology of archaebacteria that produce methane gas (on the cellular level) and from the kinetic loss of antibody titer following labeling by tritium gas exposure (on the isotopic / biochemical level and in the "humoural immunity" measurements, assisted by isotopes), possesses a significant applicability potential in clinical medicine – from the colon pathology to the gas gangrene infection agent detection [26-29].

Interface effects in gas chemistry, which can be applied in clinical and / or biochemical immunology, are very interesting. For example, verification of a specific reaction between an airborne antigen and an immobilized antibody at a gas-solid interface is the Holy Grail of the real world immunology, epidemiology and infection agent dissemination (contamination, from the standpoint of infected surface) research [30]. Also it is the Holy Grail of the atmospheric allergology, because gas-exchange following bronchial challenge with antigen in patients with extrinsic-asthma, but methacholine (well-known as a non-selective muscarinic receptor agonist in the parasympathetic nervous system) and antigen challenge upon gas exchange in allergic subject are different by mechanisms [31,32]. Consequently, it is necessary to provide a multiplexed technique for estimation of mast cell activation assessed by antigen challenge in asthmatics. It is obvious that the most sensitive approach for enzymatic assays of plasma histamines is the double-isotope technique [33]. From the above considerations one should think about the isotopic measurement techniques for two, three or more antigens or antibodies (and, consequently, about techniques, which can be realized using two, three {or more} isotopes).

Many authors of old classical articles (since 1970th) use double-antibody triple isotope RIAs, double isotope methods for the determination of antibody affinities and antigen trapping mechanism investigations [34-39]. Double-isotope techniques are actual until now, because dual isotope 3D QIQA or "DICIQA" (Dual-Isotope CryoImaging Quantitative Autoradiography) technique are useful in affimetry and qualimetry of antibody–drug conjugate distributions and payload delivery through imaging, just like the simple dual-antibody imaging (not only in static, but also in kinetic and spatiotemporal dynamic regimes [40-43]). But it is the *radioisotope* technique pull (excluding some tomography techniques, but not all [44,45]). However, it is impossible to use such techniques in clinical conditions in XXI century. Moreover, in 1970th such techniques have been preliminary approbated in veterinary but not all of them have been introduced in practice. It was not only industrial inapplicability problem, but also it was the biggest physico-chemical problem of radioimmunology: besides the antigen competition (which can be analyzed also using stable isotope labeling) and the isotope selectivity problem for antigen response monitoring or analysis there is a problem of biological fractioning of isotopes and soft matter sorption of them. Similar effects can be observed in different branches of organic chemistry, colloid chemistry and polymer chemistry – for example, kinetic isotope effects in the decarboxylation of 5-nitro-3-carboxybenzisoxazole (which can be catalyzed by antibodies and other biomimetic reactions. All described processes can be realized using non-radioactive, stable isotopes. Consequently, there is a strong need in the appropriate methods for stable isotopic measurements in chemical immunology (but not radioimmunology \ RIA) and immunometry (a term from the old articles, for example institutionalized in the second part of 2010th by Cold Spring Harbor Lab [46-54]).

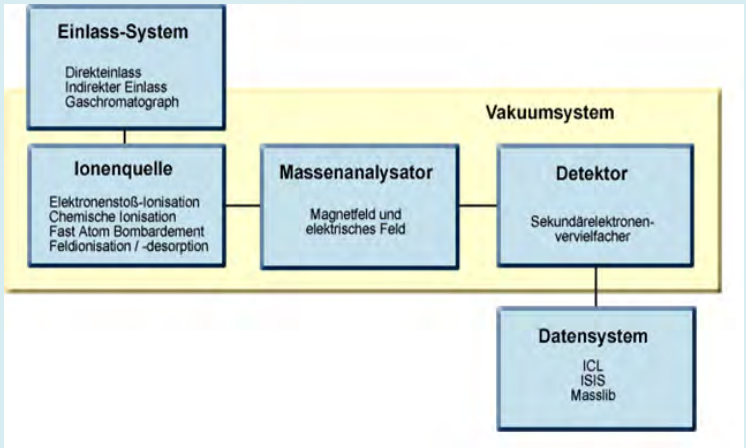


Figure 1: The principal scheme of Finnigan MAT 95.

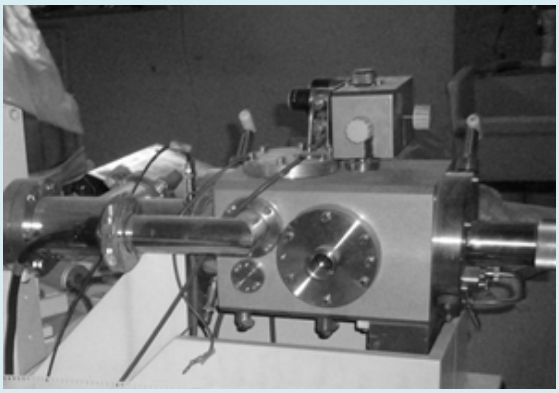
It is well known that the best technique for stable isotope analysis is isotopic mass-spectrometry. This instrument is optimal for gas phase and ultra-low concentrations and volumes of gas analytes (for example, for measurements of gas-filled microbubble-mediated delivery of antigen and the induction of immune responses gas vesicle nanoparticle utilization for antigen displaying and observations of the phagocytosis of gas-filled microbubbles by human and murine antigen-presenting cells [55-59]). The project of such instrumentation, applicable for immunometry, is presented in this article.

Tecnhical Implementation

The double focusing sector type instrument with reversed Nier-Johnson geometry Finnigan MAT 90 / 95 has been used as a general part of our setup (general scheme of this instrument is given in Fig. 1). Such devices have been used for the carbon geochemistry aims earlier [60-62]. They can also be used as instruments for gas-phase analysis in combination (tandem) with gas chromatographic devices or as the gas isotope mass spectrometer setup itself [63,64]. Finnigan MAT HDO-Euilibrator for H_2O / gas phase equilibration in hydrogen and oxygen analysis has been developed in 1990th [65]. Many modifications / upgrade options since 1980th have been implemented in some configurations of this instrument family starting from the earliest MAT models. Many papers and technical documents have been published by Finnigan engineers / constructors and related firms (for example, the most cited papers and Figure 5). The MAT family exemplars have been intensively used in Chinese works since 1980th [66-85]. It is possible to measure not only stable isotopes (including heavy ones), but also radioisotopes using MAT systems with special accessories [86,87]. It is a very good instrument until now (for example, Table 1). Such considerations can be interpreted as a prerequisite of applicability of this device in our aims (below).

Our general aims were oriented on the data-dependent analysis and transformation of interference of peaks to informative signals using deconvolution and other mathematical algorithms [88-90]. Previously our instrument has been disassembled (Figure 2). The gas chromatography section (established by "Varian 3400" gas chromatograph, which has been supported since 1980th until 2000th was disconnected before inlet withdrawing from the technical hole (Figure 3). Old computer \ data station with old dot matrix printer unit on the special chassis (Figure 4) were changed, because our project was started from the novel data station projecting, which was started on the PXI NI platform with LabVIEW supporting. The target date for the starting of novel MAT modification for immunometry was scheduled on August, 2018, but, unfortunately, the prototype exemplar has been demolished and utilized by the institute stewards \ supply managers in October, 2016. Our project documentation is confined in the room, where this system was installed previously. But it is obvious, that such measurement systems are appropriate and in the nearest future can be implemented in other conditions using alternative technical prototypes [91,92].

A



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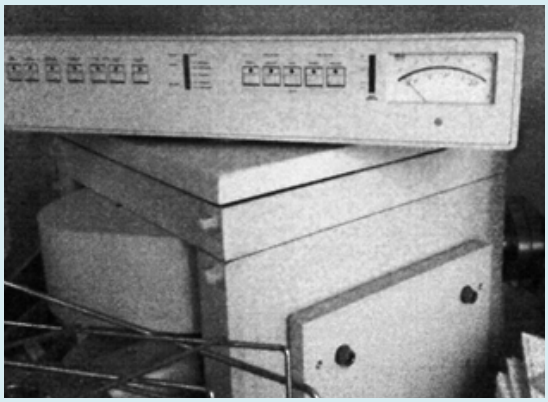

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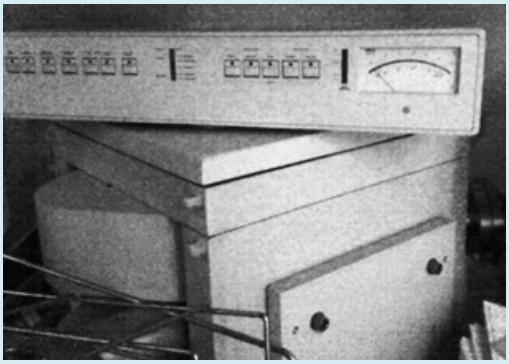

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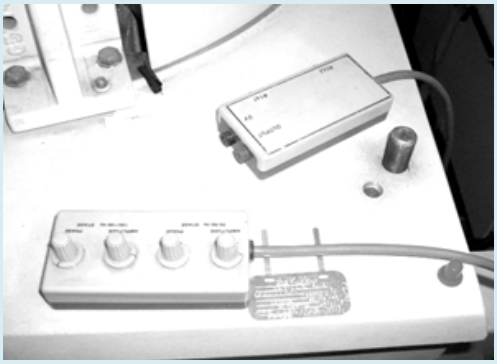

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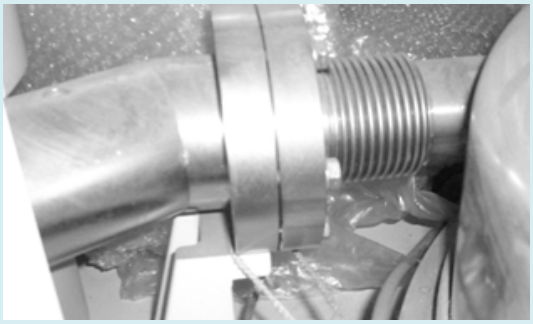

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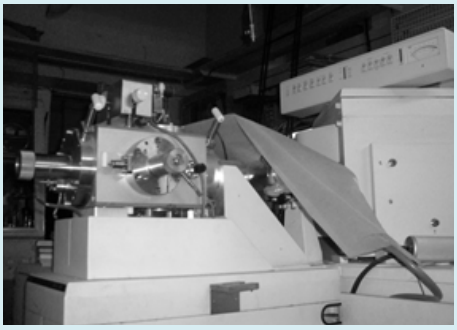

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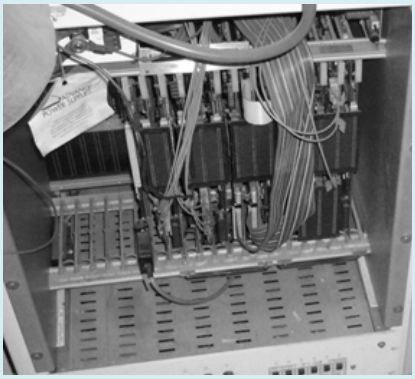

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Figure 2: Disassembled Finnigan MAT scheduled and planned for gas-phase isotopic immunometry aims.

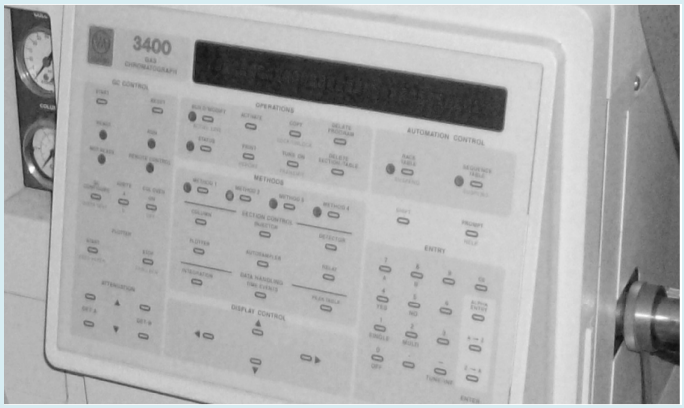
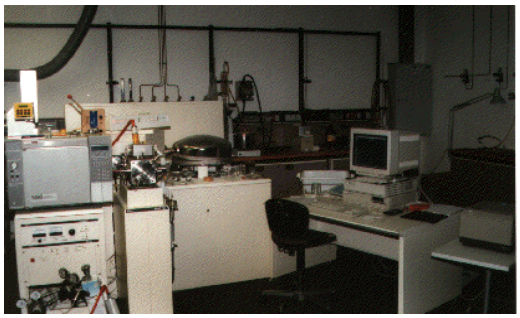
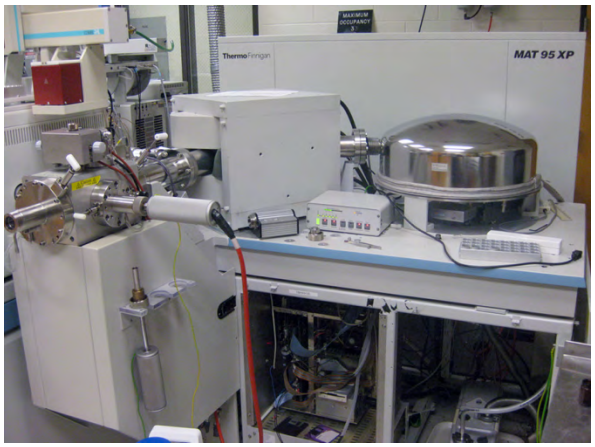
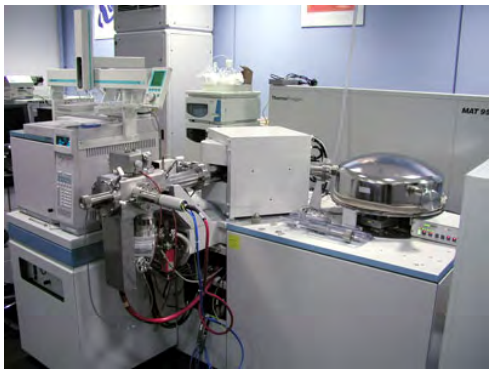


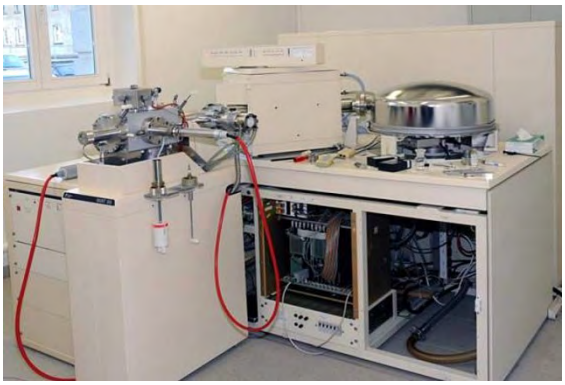
Figure 3: Gas chromatographic part of the above setup.

Figure 4: Disqualified printer and automation cable box.

Figure 5: Instruction and documentation of the MAT system.

Photography of MAT system	University or Lab and QR-codes
	Universität Oldenburg Ammerländer Heerstraße 114-118 26129 Oldenburg Finnigan MAT 95 • double focussing sector type instrument with reversed Nier-Johnson geometry • EI, CI, FD, FI, FAB, ESI • High resolution and exact mass measurement • GC/MS
	Max-Planck-Institut für Kohlenforschung Double focussing sector field MS. Equipped with ESI, FAB, EI, CI sources. Used for accurate mass measurements.
	Die Universität Bayreuth Central analytical services Finnigan MAT95 Manufacturer: Thermo Fisher Scientific Analysator: Sector field (double focusing) Mass–Range: 45 – 1000 Da (typical) Resolution: 3000 Ionization–Source: EI (Electron Ionization) Sample–Inlet: GC (Hewlett Packard 5890 Series II)

	Doppelfokussierendes Sektorfeldgerät mit umgekehrter Nier-Johnson-Geometrie (d.h. elektrostatischer Sektor hinter dem magnetischen Sektor)
	State University of New York
	International Center for Chemical and Biological Sciences.
	Organic Geochemistry Unit (OGU), Bristol Biogeochemistry Research Centre, School of Chemistry, University of Bristol, Cantocks Close,

	University of Rostock Faculty of Agriculture and Environmental Sciences
	University of Gent Amber Lab
	Państwowy Instytut Wetrynaryjny - Państowy Instytut Badawczy Zakład Radiobiologii Al. Partyzantów 57 24-100 Puławy Tel.: 81 889 30 00 Fax: 81 886 25 95

	University of Wisconsin

Table 1: Finnigan MAT localization examples in different labs.

Conclusion

Thus, in this brief review it has been shown that:

- Gas phase immunometry or gas phase immunochemistry is a promising research area with the maximum accuracy and informative results provided by gas chromatographic methods with MS detection.
- When using isotope mass-spectrometers, particularly, with Finnigan MAT application, it is possible to develop a new branch of analytical biochemistry – isotopic gas phase immunometry or gas phase isotopic immunochemistry.
- The ubiquity of Finnigan MAT-like systems in research laboratories all over the world makes it possible to continue the above studies and to develop the ideas described.

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