Institution: Loughborough University

Unit of Assessment: B10 Mathematical Sciences

Title of case study: Improved modelling of ion dynamics in the Thermo Scientific Orbitrap™ mass analyser using Hamiltonian perturbation theory

1. Summary of the impact (indicative maximum 100 words)

This case study describes the impact of research at Loughborough University from 2009-2012 into the mathematical modelling of the dynamics of ions using perturbation theory of Hamiltonian systems of equations. Outcomes from this research have been incorporated into software used for the performance modelling of a series of high-precision Fourier Transform Mass Spectrometers manufactured by Thermo Fisher Scientific GbmH and branded as Orbitrap™ with an average price $0.5 million. The derived methodology reduces the time of numerical modelling of the behaviour of charged particles in an Orbitrap™ instrument by a factor of 100 to 1000. This reduction is of significant benefit to the Life Science Mass Spectrometry, Scientific Instrumentation Division of Thermo Fisher Scientific and indirectly the users of the instrument.

2. Underpinning research (indicative maximum 500 words)

Perturbation theory of Hamiltonian systems is a well-developed mathematical subject with immense applications. One classical domain of application of this theory is the description of the dynamics of charged particles in electromagnetic fields. Professor Anatoly Neishtadt, an employee of Loughborough University from March 2007, has expertise both in the mathematical aspects of Hamiltonian perturbation theory and in its applications. References **3.1-3.5** describe research into the motion of charged particles in different electromagnetic field configurations using perturbation theory of Hamiltonian systems that was conducted at Loughborough University in 2009-2012.

In references **[3.1-3.4]** the dynamics of a charged particle under the action of an electromagnetic wave in plasma with a background uniform magnetic field is studied. The possibility (in the framework of the considered model) of unlimited acceleration of charged particles due to capture into resonance with such a wave is established for the first time. The methodology of **[3.1-3.4]** was used in (the most significant for this case study) paper **[3.5]** for the mathematical modelling of ion dynamics in the electrostatic field of the Orbitrap™ mass spectrometer. This paper is the result of a collaboration with a group of physicists and applied mathematicians from Thermo Fisher Scientific GbmH (D. Grinfeld, A. Makarov, E. Denisov) and A.M. Prokhorov General Physics Institute, Russian Academy of Sciences (M. Monastyrskiy, M. Skoblin). The authors have suggested the use of Hamiltonian perturbation theory for the description of the motion of charged particles in Fourier Transform mass spectrometers manufactured by Thermo Scientific GbmH and branded as Orbitrap™.

Orbitrap™ is a trap for ions. In this trap ions cycle around the axis of the trap and move back and forth along this axis. The use of Orbitrap™ in mass spectrometry is based on measuring the ions' axial oscillation frequency. Peaks of the Fourier spectrum of the registered electric signal correspond to assortments of ions with different mass/charge ratios. In an ideal Orbitrap™, axial motion of an ion is harmonic with the frequency independent of the ion's energy and inversely proportional to the square root of the mass-to-charge ratio. This allows the identification of different sorts of ions. This fundamental property of an ideal ion trap is corrupted by perturbations arising from the presence of the ion injection aperture, inaccuracies of electrode manufacture and Coulomb interaction between the ions (space-charge effects). Deviations of the real field from the ideal one can be treated as small perturbations. The dynamics of ions in an Orbitrap™ in the presence of perturbations may be described by a Hamiltonian system of ordinary differential equations with slow and fast variables. In reference **[3.5]** the averaged Hamiltonian motion equations are derived through averaging over fast variables. The obtained equations contain only slowly changing variables. The use of these derived equations significantly reduces the time of numerical modelling of the motion of the ions in the Orbitrap™ by a factor of between 100 to 1000, with the simulation accuracy exceeding that of direct trajectory tracing.

3. References to the research (indicative maximum of six references)

3.1. Neishtadt A, Artemyev A, Zelenyi L, Vainchtein D, (2009), Surfatron acceleration in electromagnetic waves with low phase velocity, *JETP Letters*, 89(9)**,** 441-447, DOI: 10.1134/S0021364009090045

3.2. Artemyev A, Neishtadt A, Zelenyi L, Vainchtein D, (2010), Adiabatic description of capture into resonance and surfatron acceleration of charged particles by electromagnetic waves, *Chaos*, 20(4), 043128, DOI: 10.1063/1.3518360

3.3. Artemyev A, Vainchtein D, Neishtadt A, Zelenyi L (2011), Resonant acceleration of charged particles in the presence of random fluctuations, *Physical Review E*, 84(4)**,** 046213, DOI: 10.1103/PhysRevE.84.046213

3.4. Vasiliev A, Neishtadt AI, Artemyev A, (2011), Nonlinear dynamics of charged particles in an oblique electromagnetic wave, *Physics Letters A*, 375(34), 3075-3079, DOI: 10.1016/j.physleta.2011.06.055

3.5. Grinfeld D, Makarov A, Skoblin M, Monastyrskiy M, Denisov E, Neishtadt A, (2012), Perturbation theory and space-charge ion dynamics in Orbitrap mass analyser, *Proceedings of 13th Seminar "Recent Trends in Charged Particle Optics and Surface Physics Instrumentation"*, Brno, 2012, ISBN 978-80-87441-07-7, 21-24. (Available from: http://www.trends.isibrno.cz/)

The quality of this research is recognised internationally in terms of originality, significance and rigour. Papers 3.1 – 3.4 are published in the respectable academic journals, paper 3.5 was presented at one of the main international conferences in this particular area.

4. Details of the impact (indicative maximum 750 words)

Orbitrap™ is a brand name for a series of high-precision Fourier Transform Mass Spectrometer systems produced by Thermo Fisher Scientific. The electrostatic orbital ion trap with synchronous oscillation properties was invented in 1996 by Dr. A. Makarov, who received the American Society for Mass Spectrometry Distinguished Contribution in Mass Spectrometry Award in 2008 for this development. Currently, the Thermo Scientific Orbitrap™ mass spectrometer has been produced in several versions, with an average price about US$0.5 million for one system. (Further details are commercially sensitive.) Many Orbitrap™ mass analysers have been sold to the hospitals and laboratories worldwide, but the precise number is commercially confidential.

A recent picture and description of an Orbitrap™ mass spectrometer is shown below (www.thermofisher.com).

New Thermo Fisher Scientific High Performance
Benchtop Quadrupole-Orbitrap Mass Spectrometer

Thermo Fisher Scientific introduces the Q Exactive high-performance benchtop quadrupole-Orbitrap LS-MS/MS. It is the first commercially available instrument to bring together quadrupole precursor selection and high–resolution accurate mass (HR/AM) Orbitrap™ mass analysis to deliver high confidence quantitative and qualitative (quan/qual) workflows. With innovate HR/AM Quanfirmation™ capability, the Q Exactive™ mass spectrometer makes it possible to identify, quantify and confirm more trace–level metabolites, contaminants, peptides and proteins in complex mixtures in one analytical run. Unlike other technologies, high confidence results are obtained without sacrificing MS/MS sensitivity, mass resolution or quantitative reproducibility.

Features

- Resolving power up to 140.000
- Maximum scan speed 12 Hz
- Intra – scan dynamic range > 5000:1
- Quadrupole mass filter
- Spectral multiplexing for enhanced duty cycle
- S-Lens ion source for increased sensitivity

Mathematical modelling has had a significant impact on the design of the Orbitrap™ device.

The results of reference **[3.5]** on Hamiltonian perturbation theory of the motion of charged particles had been used since 2011 by the Life Science Mass Spectrometry, Chromatography and Mass Spectrometry Division (CMD) of Thermo Fisher Scientific (Bremen) GmbH, for Orbitrap™ mass spectrometer performance modelling. The mathematical techniques were implemented in the MASIM-3D software package in 2012. The averaged motion equations describe the resonant interactions of many ions of the same or close masses. The calculation time decrease gained from averaging ensures the modelling of a reasonably large number of ion macro-particles (up to ~ $2x10^3$) to reveal the sophisticated space charge effects of self-bunching and coalescence in an Orbitrap™ mass spectrometer. The coalescence is a synchronization phenomenon when ions of close masses move with the same frequency. Thus they create one peak on the observed Fourier spectrum and cannot be identified/distinguished using this spectrum. Numerical analysis of ionic motion close to the threshold of synchronisation allows reliable estimation of the mass resolving power limitation in an Orbitrap™ mass spectrometer. The calculated dependence of the synchronisation threshold as a function of intentionally introduced small static perturbations allows the coalescence effect to be controlled.

The modelling of space-charge effects in the Orbitrap™ mass spectrometer by direct tracing of multiple interacting ions is an extremely computationally demanding and time-consuming task.

Obtaining the required accuracy is a major challenge. However, using the averaged Hamiltonian equations derived in **[3.5]** allows specialists at Thermo Fisher Scientific to model the space-charge effects in reasonable computer time with appropriate accuracy. This allows them to try many variations of the parameters in order to determine the necessary values to optimise the Orbitrap™ mass spectrometer's performance.

The beneficiaries of the research are Thermo Fisher Scientific and indirectly their customers in healthcare research and industry. Orbitrap™ mass spectrometer is used in many hospitals and laboratories in the UK and worldwide, in particular for drug monitoring and food safety analysis.

Thermo Fisher Scientific is a large precision healthcare equipment global company with offices and operations in most countries around the world, and 2013 revenue guidance between $12.83 billion and $12.95 billion.

5. Sources to corroborate the impact (indicative maximum of 10 references)

The following sources of corroboration can be made available at request:

5.1. Letter from: Director of Global Research for Life Science Mass Spectrometry,

Thermo Fisher Scientific (Bremen) GmbH

Advanced Mass Spectrometry

Bremen

Germany