Development of the Next Generation of On-line Radiochromatography Detectors

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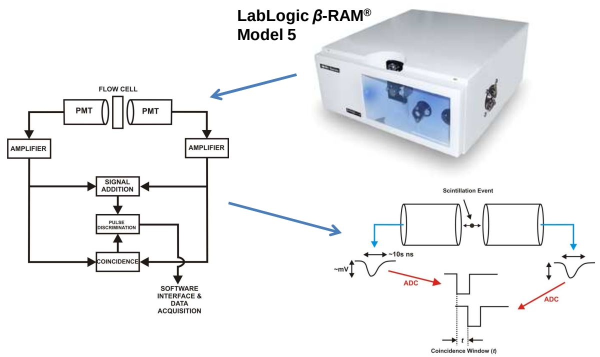
Abstract

Since the 1980s, on-line radiochromatography (RC) measurements have formed an integral part of metabolite profiling studies and are nowadays coupled with advanced HPLC, UHPLC and MS analysis techniques. Currently, the commercially available on-line detectors are being pushed to their operational limits as demands for **better sensitivity** and **higher resolution** are ever-increasing, along with the added pressure from desirable **shorter run-times**. Part of this demand is being fuelled by the necessity to work with much **lower levels of β-radioactivity** and so a significant improvement in the signal to noise ratio will be of paramount importance in the near future. In this work, we describe and present some experimental results of an on-going research collaboration that aims to identify key areas for on-line radio-detector instrument development and improvement through appealing to both the fundamental physics of the measurement process and the latest technological advances. The collaboration is between the **University of Sheffield's Department of Physics and Astronomy** and **LabLogic Systems Ltd.** and is funded by the UK Government's Knowledge Transfer Partnership (KTP) initiative. The culmination of the work will see future generations of LabLogic's β-RAM® on-line radiochromatography detector leading the way in terms of resolution and reproducibility, as well as providing a detailed insight into the fundamental scientific processes that are in play.

On-Line LSC and its Limitations



Dark Counts = $2N_1N_2\tau$

Dark count rate of each detector **Coincidence window (~10s ns)**

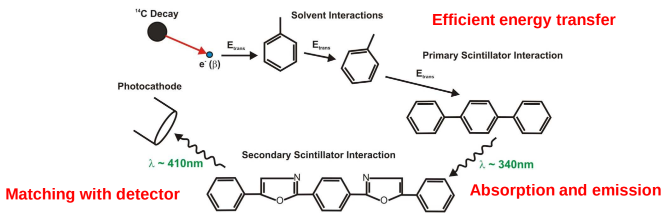
The primary objective of this work is to improve the limit of detection by an order of magnitude to enable **10 dpm** to be resolved in a single chromatography peak. New methods and technologies are being sought to maximise the detected signal and minimise the sources of noise.

The main limitations affecting on-line LSC/RC measurements are:

- **Unwanted sources of background**
- **Aging detector and signal processing technology**
- **Compatibility with advancing HPLC/UHPLC systems**
- **Sub-optimal chromatographic separation**
- **Due to the dynamic nature of the measurement process**

Solutions

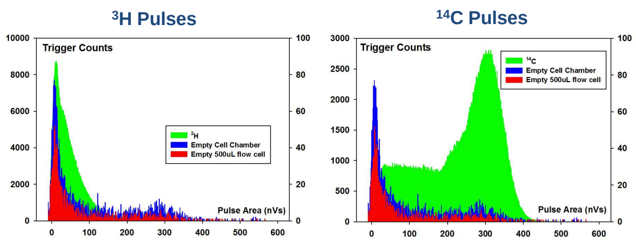
Understanding the Detection Process



Differentiation of Sources of Noise and Background

Pulse area analysis may be used to good effect in order to determine which events are due to the decay of the β-isotope and which arise from random coincidence events.

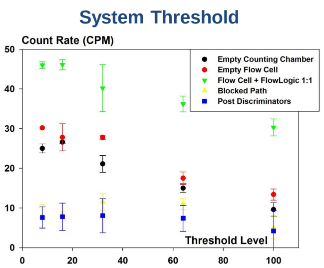
Pulse area → Charge → β Energy

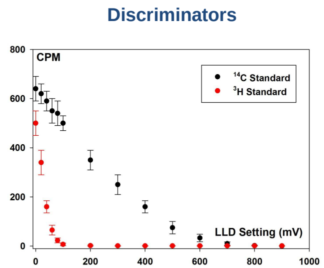


This type of **real-time analysis** enables different isotopes to be identified in complex samples and may bring benefits to other applications such as environmental monitoring.

Eliminating Detector Cross-talk

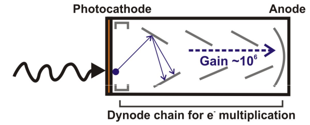
The main source of random coincidences is from **'cross-talk'** between the PMT detectors. Cross-talk arises from the **emission of thermal electrons** from the photocathode of the PMTs and as a result of the **geometry** of the measurement. Current practice attempts to eliminate these via pulse height comparison, reduced operating HV and discriminator window settings.





New Detector Technologies

The limit of detection (LOD) can be improved through improved detector performance and better matching between the detector and sample/scintillant cocktail. Existing photomultiplier tube (PMT) detectors have an efficiency of **~25%**. This can be increased to **~45%** with state-of-the-art PMTs **[1]**. Semiconductor-based detectors are a consideration for the future **[2]**.



Quantum Efficiency = N/P

N = No. of incident photons
P = No. Of photoelectrons at photocathode

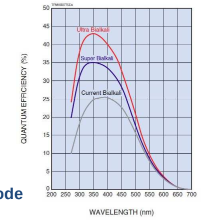
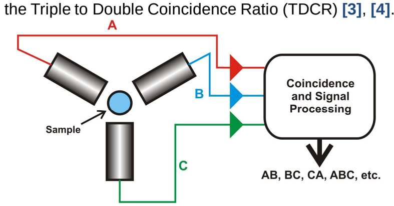


Image Source: Hamamatsu Photonics

In order to eliminate detector cross-talk fully, and alternative counting geometry may be necessary. One of the most promising techniques employs three detectors and exploits the Triple to Double Coincidence Ratio (TDCR) **[3]**, **[4]**.

TDCR = T/D:
Triple Events/
Double Events



Signal Capture and Processing

Modern, digital signal processing will be used to improve the sampling rate and offer real-time pulse analysis to improve SNR and aid reproducibility.

UHPLC Compatibility

Changing market demands and the rapid uptake of UHPLC analysis means that improved compatibility with such systems is a priority. With this in mind, **fluid flow** is also being considered to optimise the instrument for higher working pressures and reduced sample volumes.

New Applications

Whilst the primary target markets are the pharmaceutical and CRO sectors, the wide applicability of the technology will allow instruments to be used in a number of new markets. Such applications include:

- **Tritium water monitoring**
- **Isotope identification in complex samples**
- **On-line monitoring in nuclear power stations**

References

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[2] D. Renker and E. Lorenz (2009), Advances in solid state photon detectors, *J. Inst.*, vol. **4**, P04004 .
[3] K. Pochwalski et al., (1988), Standardization of Pure beta Emitters by Liquid-Scintillation Counting, *Appl. Radiat. Isot.*, vol. **39** (2), 165-172.
[4] L. C. Johansson and J. P. Sephton, (2010), Validation of a new TDCR system at NPL, *Appl. Radiat. Isot.*, vol. **68**, 1537-1539.

Acknowledgements

KTP Grant Ref. 7294

Knowledge Transfer Partnerships

Technology Strategy Board
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