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## Background

2025 marks the 10<sup>th</sup> anniversary of the formal establishment of the International Society for Clinical Spectroscopy (CLIRSPEC)<sup>1</sup> as a Private Company Limited by Guarantee on the Registrar of Companies for England and Wales on 30<sup>th</sup> June 2015. The venture was progressed through the UK Engineering and Physical Science Research Council (EPSRC) Clinical Infrared and Raman Spectroscopy for Medical Diagnosis Network (also CLIRSPEC, 2014–2017). As an international society, CLIRSPEC is a non-profit organisation, with a stated objective to act as a platform for those individuals, teams and organisations wishing to promote the translation of spectroscopy into the clinical environment, for the general benefit of patients; for example, to improve patient diagnosis and prognosis. The Memorandum of Association of the society<sup>2</sup> also includes aspirations to;

- Promote a broader representation (e.g. of gender and nationality) of individuals working within the field of clinical spectroscopy;

- Organise national and international public lectures, meetings, debates and conferences;
- Engage in outreach activities of all sorts;
- Participate in, support, fund and disseminate research, innovation and other activities relating to the objectives;
- Award scholarships and bursaries raised from third party contributions to enable attendance at, and travel to, any national or international congresses related to the (society)

In reality, the measure was deemed necessary to protect the interests of the growing clinical spectroscopy community, largely academic based, which had evolved through a series of conference events, and national and international collaborative networks, largely based on the drive of individuals, who were subjected to increasing burden of workload and financial commitment.

## Historical perspectives

The historical development of vibrational spectroscopy, and specifically biological applications, has been reviewed by Henry Mantsch, one of the early pioneers of the field.<sup>3,4</sup> Beginning in 1997, the so-called Berlin IR workshop,<sup>5</sup> hosted by Dieter Naumann and Peter Lasch at the Robert Koch Institute, was initially targeted at IR spectroscopic analysis of pathogens and microorganisms, but laterally expanding to include vibrational spectroscopy, and clinical applications more broadly, did much to crystallise and sustain a kernel of the vibrational spectroscopy community, particularly in Europe. The first SPEC Conference in Winnipeg (2000) has also been flagged as a key milestone. Under the tagline of “Shedding new light on disease”, the event precipitated the biennial series of conferences which was continued through similar events in Reims (2002), Newark (2004), Heidelberg

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(2006), São José dos Campos (2008), Manchester (2010), Chiang Mai (2012), Kraków (2014), Montreal (2016), Glasgow (2018), Monterey (2020 cancelled due to COVID-19), Dublin (2022) and most recently in Ioannina (2024). Starting in 2010, the proceedings of the conferences have been published through special issues of *Analyst*.<sup>6–11</sup>

A significant impetus, particularly in Europe, was the EU FP6 Special Support Action (SSA) Diagnostic Applications of Synchrotron Infrared Microscopy (DASIM–2005–2008) which, although targeted towards specific aspects of the field, included, for example a Raman Working Group, and clinical stakeholders and international advisors, and thus brought together key players in biological applications of vibrational spectroscopy through a targeted programme to identify key challenges. Although the programme did not fund research *per se*, the collaborative effort led to, for example significant developments in understanding and alleviating artefacts in both IR<sup>12–14</sup> and Raman<sup>15–17</sup> microspectroscopy. Above all, DASIM provided a platform for the emerging biospectroscopy community to begin to explore and establish consensus options on aspects of sample processing and presentation, instrument calibration, data preprocessing and analysis. As a deliverable of the SSA, the multi-author DASIM Book sought to provide a practical approach to biomedical applications of spectroscopy, from a clinical perspective.<sup>18</sup>

Efforts to maintain the momentum of the community consolidated by DASIM in Europe through applications to Marie Curie (now Marie Skłodowska-Curie) Training Networks and COST Actions were unsuccessful, and any collaborations were maintained largely on an informal, individual basis. In 2013, the UK EPSRC funded the national network, CLIRSPEC (2014–2017), bringing together expertise and stakeholders from the academic, clinical and instrumental manufacturers sectors across the UK, with international advisors. In addition to facilitating short term interlaboratory research exchanges, the network held two very successful conferences, in Exeter (2015) and Manchester (2017), and coordinated the Faraday Discussions meeting “Advanced Vibrational Spectroscopy for Biomedical Applications” in Cambridge, 2016.<sup>19</sup> As an integral part of its mission in training and development of early stage researchers, the Network instigated the CLIRSPEC Windermere Summer School in 2015, which continues to run annually, now under the umbrella of the CLIRSPEC International Society.

The legal foundation of the International Society CLIRSPEC was funded as an exit strategy of the UK EPSRC Network, and, as it was officially founded in June 2015, the two versions of CLIRSPEC overlapped until 2017, providing continuity. During this time, the activities also interacted strongly with those of the EU COST Action Raman4Clinics (2015–2018), which, amongst other outputs, produced two large-scale interlaboratory trials assessing the reproducibility of Raman<sup>20</sup> and surface enhanced<sup>21</sup> Raman.

The International Society adopted the SPEC series of conferences as its flagship, and, although the initial announcement of the impending foundation of the society was made at

SPEC 2014 (Krakow), official association of the SPEC began with SPEC 2016 (Montreal), continuing with SPEC 2018 (Glasgow), SPEC 2020 (Monterey – cancelled due to COVID), SPEC 2022 (Dublin) and SPEC 2024 (Ioannina). Over the past ten years, the society has also expanded its dissemination brief to encompass association with a range of other conference and workshop series;

In November of 2017, CLIRSPEC became a member of the Federation of Applied Chemical and Spectroscopy Societies (FACSS – <https://facss.org/>), and thus has been formally represented in the annual SciX (<https://facss.org/scix-annual-conference>) programme since then.

In August 2019, CLIRSPEC teamed up with the Japan Association of Medical Spectroscopy (<https://medical-spectroscopy.jp/>) to support the CLIRSPEC Summer School in ASIA, in Kobe City (<https://sci-tech.ksc.kwansei.ac.jp/clirspeccs/>).

In October 2019, CLIRSPEC became co-organiser of the 12<sup>th</sup> annual Workshop on “FT-IR Spectroscopy in Microbiological and Medical Diagnostics” hosted by the Robert Koch-Institute, Berlin, Germany.

CLIRSPEC was also an official organiser of the 11<sup>th</sup> (online-2021) and 12<sup>th</sup> (Kraków-2023) editions of the International Conference on Advanced Vibrational Spectroscopy (ICAVS).

In April 2021, the UK EPSRC accepted the proposal for the Grand Challenges in Healthcare Network, “Integrating Clinical Infrared and Raman Spectroscopy with digital pathology and AI: CLIRPath-AI” (<https://clirpath-ai.org/>). In terms of spectroscopic expertise, the network is an evolution of the UK EPSRC CLIRSPEC network, and has integrated the CLIRSPEC Windermere Summer School with a series of sandpit events exploring topics for short pump-prime projects, over the period 2021–2025, culminating in the final Network conference in May 2025.

## Developments of state of the art

The evolution of the state of the art of clinical spectroscopy has previously been mapped out according to realms of clinical applications,<sup>22,23</sup>

### 1. *In vivo*;

a. Intraoperative characterisation of tumour resection margins

#### b. Endoscopic probes for disease detection

In both areas, the availability of near infrared optical fibre probes has favoured the use of Raman spectroscopy for *in vivo* applications, 1.a. having been demonstrated as early as 2010,<sup>24–26</sup> 1.b. in 2015.<sup>27,28</sup> The dominance of Raman in such applications has persisted, such that Raman probes for oesophageal cancer diagnosis are entering the stage of clinical trials,<sup>29</sup> and coherent Raman techniques have been increasingly explored.<sup>30</sup> A marked indication of progress towards clinical translation is the commercial development of both incoherent and coherent modalities for intra operative and endoscopic applications.<sup>31–33</sup>



## 2. *Ex vivo*;

### a. Spectroscopic histopathology

The emergence of focal plane array technology meant that, by 2013, large scale ( $\text{cm}^2$ ) biopsies could be screened using FTIR microscopy, albeit on timescales of  $>10$  hours.<sup>34</sup> Progress was also made in the use of glass substrates which, although it limits the infrared spectral range, shows promise for simple tissue characterisation<sup>35,36</sup> and cellular analysis.<sup>37,38</sup> It has been demonstrated, however, that the full spectrum is not required to maintain diagnostic accuracy,<sup>39</sup> and the emergence of mid infrared tuneable quantum cascade laser systems prompted the exploration of discrete frequency IR imaging.<sup>40,41</sup> Further significant advances have been made through the use of deep learning methods, for example to reconstruct incomplete spatial domain IR data recording, which enables more rapid sample scanning.<sup>42</sup> Coherent Raman techniques have also been used for rapid histopathological screening, albeit also at discrete frequencies.<sup>43</sup> Ratios of Raman signals reflecting the relative lipid and protein contents can provide H&E like images, and convert the Stimulated Raman Scattering (SRS) signals into virtual H&E slides.<sup>44</sup> The Stimulated Raman Histology technique is now commercially available to image fresh tissue specimen without sectioning or staining, enabling near real-time histologic evaluation in the treatment room.<sup>45</sup>

### b. Spectroscopic cytology

Although much of the pioneering work in spectrocytology was performed with IR absorption microscopy,<sup>46,47</sup> Raman microspectroscopy has become the more prominent choice for cytological applications in, for example cervical and oral cancer screening.<sup>48–50</sup> Hormonal effects,<sup>51</sup> blood contamination,<sup>52</sup> viral infection<sup>53</sup> and the influence of other confounding factors have been addressed, and protocols standardised to integrate as best as possible in the clinical workflow.<sup>54</sup> Process automation has been explored for high throughput screening,<sup>55</sup> and broadband CARS has been demonstrated for rapid classification based on individual cellular analysis.<sup>56</sup>

### c. Liquid biopsies

An application which has seen particular growth over the past decade is that of diagnostic screening of liquid biopsies. The initial work, demonstrating the ability of ATR-FTIR spectroscopy of dried blood serum to distinguish between cancer *vs.* non-cancer, metastatic cancer *vs.* organ confined, brain cancer severity and organ of metastatic disease with high sensitivities and specificities,<sup>57,58</sup> has been progressed towards commercialisation,<sup>59</sup> as have the applications of Raman analysis of hydrated serum for colorectal cancers.<sup>60</sup> Of note also is the use of ATR-FTIR spectroscopy for the determination of malaria parasitaemia in whole blood samples, demonstrated in field trials in austere environments proving the robustness and capability of serum biofluid diagnostics.<sup>61–63,64</sup>

## 3. *In vitro*;

### a. Drug screening and companion diagnostics

Applications of vibrational spectroscopy for *in vitro* screening of toxicants, including nanoparticulate materials,<sup>65,66</sup> chemotherapeutic agents,<sup>67–69</sup> radiation treatment,<sup>70–72</sup> stem cell differentiation<sup>73</sup> and virology,<sup>74</sup> have continued. Increasingly,

attention has been devoted to kinetic studies of the cellular interactions, and subsequent cellular responses.<sup>75–78</sup> As the capabilities for analyses advance towards real-time, full spectral, subcellular visualisation of the cellular metabolism, the demands on the ability to data mine and interpret the responses also increases.<sup>79–81</sup>

In terms of clinical applications of vibrational spectroscopy, a somewhat overlooked area which has emerged over the past decade is that of analytical quality control in pharmaceutical dispensing,<sup>82–85</sup> and blood storage and transfusion.<sup>86,87</sup> Within the same time period, the world has seen an increasingly prominent usage of IR and Raman spectroscopies in security screening,<sup>88</sup> a development which may have a knock-on effect on clinical uptake.

### b. Molecular diagnostics

Molecular diagnostics approaches are becoming increasingly important, particularly in the drive towards personalised medicine.<sup>89</sup> Although deep learning methods such as convolutional neural networks (CNN) are being increasingly used to analyse infrared and Raman spectra of biopsy tissue, they are often treated as a black box and it is difficult to associate specific spectral features with disease state.<sup>90,91</sup> This is a problem, since the European Union Artificial intelligence act deems the use of AI in medical diagnostics as high risk.<sup>92</sup> As a consequence, the act requires that the system must be sufficiently transparent to end users such as clinicians to enable them to understand, (i) how the AI works, (ii) what inputs it uses and most importantly in this context, (iii) the basis for its recommendations. This means that the AI has to be explainable, which, in most cases, means linking the spectral features to specific known molecular biomarkers. One example of this is the study by Goertzen *et al.* which showed that QCL data from lung cancer tissue could be linked with specific mutations (KRAS, EGFR, and TP53), with 95% sensitivity and specificity.<sup>93</sup> However, the concentration of most biomarkers is low and the signals are convoluted with the vast array of other constituent molecules, meaning that this is incredibly challenging.

A second approach to delivering explainability is to cross reference with other biological techniques. Linking IR spectral profiles of tissue to gene expression data is an emerging direction of research, linking spectral pathology with molecular biology. An example of this is the work by Tiwari *et al.*, who were able to link infrared data to a specific gene expression profile, referred to as ECM3 (Extracellular Matrix Cluster 3).<sup>94</sup> Another approach is to link spectral imaging data with mass spectrometry data, either using secondary ion mass spectroscopy (SIMS), matrix-assisted laser desorption/ionisation (MALDI) or proteomic analysis.<sup>95–97</sup> Correlating IR signatures with proteomic data has been shown to be particularly powerful and has led to the identification of a new biomarker for bladder cancer, specifically to differentiate urocytisis with reactive urothelial atypia and carcinoma *in situ* (CIS).<sup>98</sup>

An emerging area of research that could have an eventual impact in diagnosis is the characterisation of spectral signatures of kinetic processes at a cellular level. An example of this approach is the study of Goffin *et al.*, who applied a trajectory



inference analysis of the evolution of Raman spectroscopic profiles of the differentiation of adipocyte cells.<sup>99</sup> The application of cluster analysis enabled the identification and differentiation of the Raman spectral profiles of the different cell stages, which were then arranged in the sequence of the trajectory inference analysis. More recently, Kobayashi *et al.* demonstrated the prediction of single-cell RNA expression profiles in live cells by Raman spectroscopy.<sup>100</sup> Using the example of mouse stem cell differentiation, neural network prediction models were trained by correlating the Raman spectroscopic subcellular analysis profiles with corresponding single-molecule fluorescent *in situ* hybridisation (smFISH) profiles of nine anchor genes. These profiles were then correlated with those of the selected genes in single cell RNA sequencing analysis, enabling the evolution of the genomic profiles to be tracked in real-time, *in situ* in live cells, as they underwent the differentiation process. The analysis also yielded importance scores of the different features of the Raman spectra in predicting the cell-related marker genes, although the evolution of these features along the trajectory was not resolved. The use of deep learning techniques to associate label free spectroscopic "spectralomic" signatures with cellular events and/or processes may therefore open up avenues for a more holistic application of the techniques.<sup>81</sup>

#### 4. Data processing and analysis;

Multivariate statistical analysis, including by machine and deep learning algorithms, continues to be the bedrock of clinical spectroscopy, and AI protocols for, for example, de-noising, and enhancing spatial resolution have emerged.<sup>42,101–103</sup> Multiblock and data fusion techniques are becoming increasingly explored, combining data from different techniques,<sup>104</sup> or biological samples.<sup>105,106</sup>

Sharing of datasets and analysis protocols has been high on the agenda of the society since its foundation. In addition to making data downloading, preprocessing and analysis scripts available through its Members' website,<sup>1</sup> the society established an open access Zenodo community.<sup>107</sup> Amongst the stated goals are to;

- Develop a standard data transfer format to allow free and easy dissemination of data between network members enhancing collaboration and efficiency of research funding
- Investigate the technological, cultural, ethical and IP issues in order to enable data sharing and reuse

In an effort to further embed the Findable, Accessible, Interoperable, and Reusable (FAIR) guiding principles for data management<sup>108</sup> in the biospectroscopy community, the FAIRspectra initiative, launched in 2023 aims to; (i) develop an open file format for hyperspectral data produced by vibrational spectroscopies and mass spectrometries, and (ii) explore the metadata requirements for sharing such data.<sup>109</sup>

## State of play and future perspectives

The past decade has been a period of rapid instrumental development, which continues to address limitations of spectroscopic sampling speed, spectral and spatial resolution, not

just for short term clinical applications, but for more fundamental research, exploring the limits of label-free spectroscopic imaging and analysis. Coherent Raman Imaging is already integrated into established commercial optical microscopic platforms,<sup>110</sup> and commercial broadband systems are emerging.<sup>111</sup> QCL based IR microscopy is well established,<sup>112,113</sup> and the pulsed nature of the QCL systems has opened up a new field of hybrid techniques which provide IR absorption microspectroscopy with lateral resolution on the scale of tens of nanometers.<sup>114,115</sup> Of particular note are the photothermal systems, in which the IR absorption and Raman scattering spectra can be recorded from the same spot, with optical resolution (<1 μm), the newer models of which also integrate fluorescence microscopy.<sup>116</sup>

While the past decade has seen continued advancement of the spectroscopic and data analytical techniques available to the clinical spectroscopy community, a notable feature of that development is the emergence of commercial enterprises, either customising existing instrumentation,<sup>59,60</sup> or developing bespoke solutions for clinical applications.<sup>31,33,45,117,118</sup> These solutions are on the brink of realisation of clinical translation.<sup>29,119,120</sup>

As the efforts of the community to translate biospectroscopy into real clinical applications, a marked evolution has been that of the language used, which now includes aspects of clinical workflow and health economics,<sup>121</sup> patient perspectives,<sup>122</sup> and in turn reflects an increased awareness of the demands of the clinical sector. This has been developed through continued engagement with, and advocacy of, clinical practitioners.<sup>123–125</sup> In this context, the UK EPSRC Healthcare Technologies Grand Challenges network CLIRPath-AI specifically aims to synergistically combine expertise in clinical spectroscopy with that of Digital Pathology and Artificial Intelligence to progress and maximise the impact on healthcare. Accelerating the roll out of digital pathology for cancer screening in the National Health Service is high on the agenda of the UK Government,<sup>126</sup> and among the investments are the National Pathology Imaging Co-operative (NPIC), a centre of excellence in digital pathology and AI,<sup>127</sup> and the Pathology Image Data Lake for Analytics, Knowledge & Education (PathLake),<sup>128</sup> aiming to address the demand for AI-driven diagnostics to increase efficiency in pathology reporting and improve patient outcomes. Concerted engagement with such communities increases the visibility and profile of label free spectroscopic imaging for diagnostic applications, towards meaningful clinical translation.

## Conflicts of interest

The authors of this paper are the current directors of the International Society for Clinical Spectroscopy.

## Data availability

There is no data associated with this perspectives paper.



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