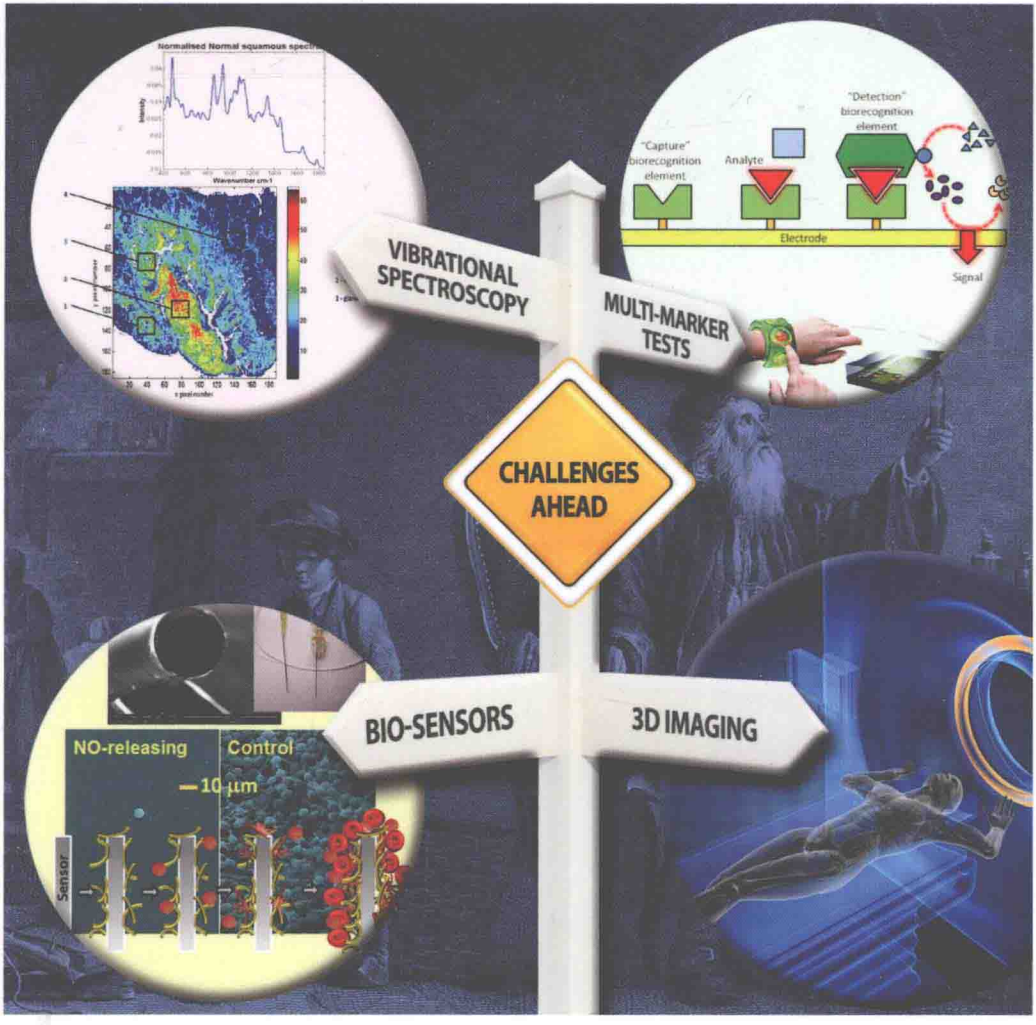
RSC Detection Science

Edited by Pankaj Vadgama and Serban Peteu

Detection Challenges in Clinical Diagnostics



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Detection Challenges in Clinical Diagnostics

Edited by

Pankaj Vadgama
Queen Mary University of London, UK
Email: p.vadgama@qmul.ac.uk

and

Serban Peteu
National Institute for R&D in Chemistry and Petrochemistry, Bucharest, Romania
Email: sfpeteu@umich.edu

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Detection Challenges in Clinical Diagnostics

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Preface

There have been quite a number of topical texts and reviews published recently dealing with clinical diagnostics. So, one question to ask is why another book? This Preface hopefully provides a rationale for this. In a parallel vein, there was a belief in the idea of a "Fountain of Youth"; an aged-adult body enters the "Fountain" Service and exits with new body components, with as good-as-new regeneration. To bring this up to date, even if this was achievable, say by tissue engineering the question arises – would the insurance companies foot the bill? So not only are there residual uncertainties, even in utopia, but context is ever changing.

To return to the present topic, our aim was to bring the reader up to date within the context of rapidly evolving technology and to communicate this through the eyes of research leaders. A broad range of approaches is scoped and the diagnostics needs and bottlenecks surveyed. Both academic and industrial experts are included, all addressing robust tools for dealing with the world of *real* biological measurement – especially from the perspective of a commonly neglected expert: the end user.

Chapter 1 (by Thompson *et al.*) and **Chapter 2** (by Vadgama *et al.*) deal with Clinical Diagnostics, both in the laboratory and at the bedside, from the broader picture down to some details. There have been powerful advances in extralaboratory testing enabled by new solid-state technology encompassing reagent immobilisation and miniaturization. This is a difficult area to monitor and set standards for, because of the distributed nature of such testing across a variety of clinical sites and even the home. Laboratory analysis has taken on major advances with high throughput and small sample volumes, so polarisation between technologies that are aimed at laboratory testing *vs.* those for extra laboratory testing are inevitable.

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Analytical specificity remains a vital issue, still not fully resolved, especially for low-concentration analytes, regardless of technique, and where sample separation cannot be part of the assay system, as in say *in vivo* sensors, quite significant effort is required to redesign the basic construct. This latter owes as much to materials science and engineering as to chemistry.

Selectivity in general is discussed in Chapter 1 (by Thompson *et al.*) with specific regard to Clinical Chemistry. In the *in vivo* context, sensors need to function selectively given their exposure to unmodified samples. There is the added complication of high local protein concentration and cellular ingress at the implant site. Returning to *the selectivity challenge*, there are helpful, published techniques for electrochemical bio/sensors reviewed in Chapters 1 and 6 (Thompson *et al.*; Peteu and Szunerits), including membranes to address solute transport and interfacing issues. Ultimately, one needs to be mindful of the *trade-off* between *analytical complexity* and *slower processing* as against the goal of *high specificity*.

This issue of damaging nonspecific adsorption (NSA), represents a true Achilles heel for direct contact sensors, and is examined in detail. With biological matrices constituting highly complex solute mixtures, it becomes clear they could well prevent the detection/quantification *of target analytes present at considerably lower concentration,* outlined in Chapter 1 (Thompson *et al.*).

Early advances in this regard, though not always seen as such, are the dry reagent systems developed for glucose as illustrated in **Chapter 3** (Wang and Hu). Here, unless the integrated laminates are not tailored to whole-device function and can be produced in mass numbers, the overall transduction value cannot be realized. This chapter examines the progress and challenges of the blood-glucose biosensors. Managing one's diabetes also decreases the occurrence of its serious complications such as nephropathy, neuropathy and retinopathy. The pathogenesis of diabetes and its complications seem to be correlated with the presence of nitro-oxidative species – including peroxynitrite – potentially implicated in beta-cells destruction, as highlighted in Chapter 6 (Peteu and Szunerits).

Chapter 4 (Gaspar *et al.*) critically assess recent progress and many challenges in electrochemical detection of disease-related diagnostic biomarkers. Mostly, we have relied on biomolecules, but *aptamer technology* shows how such synthetic structures can be harnessed to give stable "readers" for biochemical targets. These are early days still for the technology, and designer aptamers bred *via* SELEX (selective evolution of ligands by exponential enrichment), should extend their repertoire. It may also be that here and elsewhere, with use of arrays, absolute selectivity will not be a necessity.

As with sampling integrity, so with continuous use sensors for monitoring *in vivo*, Chapter 5 (by Meyerhoff *et al.*), shows there is great need to *reduce biocompatibility and resultant surface fouling;* biofluids are not tolerant of foreign surfaces. ***In vivo* sensors** are, however, uniquely positioned to provide site-related information, in particular at specific extravascular, tissue locations, but face a huge safety and biocompatibility challenge. The fact that this has been resolved in some cases raises the possibility of broader forms of monitoring

systems. Even using early proof-of-concept systems, it may yet be possible to pick up biological signatures that arise from wider disease sets.

Chapter 5 (Meyerhoff *et al.*) especially scrutinizes the challenges for **sensors long-term biocompatibility**. In spite of the great sensors advances *in vitro*, the commercial development of *implantable* chemical sensors has reached a bottleneck. So much so, that, even *with* the FDA-required recalibration the output of devices, is still *not considered reliable enough*. Special coating materials able to say *attenuate the activation of platelets* or materials able to *inhibit the inflammatory response* will become important.

In the case of more exotic short-lived radical species such as *peroxynitrite* (often $\leq$1 s lifetime) featured in **Chapter 6** (by Peteu and Szunerits) measurement in real environments will be difficult. For species such as peroxynitrite, quantification poses a whole new level of measurement uncertainties, yet they are important: cell signalling, reactivity and tissue damage are mediated by such short-lived radicals. Mitochondrial oxidation is itself a free-radical generator. Interestingly, *nitric oxide*, *superoxide*, the precursors of *peroxynitrite, and peroxynitrite* itself have been dubbed "the *good*, the *bad* and the *ugly*" because of their tissue-level effects. This chapter illustrates the chemical diversity of such reactive species and the way in which electrochemical interfaces and sensor chemistry could track some of these, as a glimpse into future clinical use.

The biomachinery resulting in ineffective haematopoiesis and augmented leukaemia risk in *myelodysplastic syndromes* is largely known. However, one major challenge illustrated in **Chapter 7** (by McNamara *et al.*) is how to correctly classify and "risk stratify" the patients. Molecular biology assessment could help as diagnostic tools. So often, the right diagnosis – offered early in the game – will affect morbidity and survival.

Chapter 8 (by Barr *et al.*) describes *Raman for noninvasive early cancer diagnosis*. Early histological appearances may be difficult to categorise, and there is less interobserver agreement. Some changes may not even be evident by traditional histology, moreover; diagnosis is expensive, time consuming and requires required tissue biopsy. For the specific case of oesophageal neoplasia, there is evidence that a Raman signature can identify molecular change prior to morphological aberrations.

Raman spectroscopy can deliver high sensitivity for degenerating, premalignant, oesophageal epithelium. The gain would be objectivity, speed and a real-time assessment for early removal of dysplastic tissue and follow up. Raman-based fibre-optic interrogation has potential as an *in situ* surgical adjunct.

Signal handling with arrays is well exemplified in **Chapter 9** (by Kendall *et al.*). Any opportunity to create multiple arrays should be taken, as this adds depth to measurement. Here, for volatiles analysis the power of pattern recognition is well demonstrated. Undoubtedly the principles can be extrapolated to other modes of measurement, including where selectivity and drift are challenges, be it *in vivo* or *in vitro*.

Another overarching challenge in clinical diagnostics: the critical need to provide *information not just data*. With ease of data generation, it could be said

that there is too much data for the clinician to deal with, especially if it is real time as with *in vivo* monitoring devices. Herein lies the problem of what the data is really for; if it is a medical defence strategy it becomes a waste of finances, but if behind the data there is a genuine quest for what the bio/pathological implications might be, then the data becomes of considerably greater value.

As with any scientific quest, one might consider this to be analogous to a person searching for their home keys under a streetlamp, even though these might have been dropped somewhere else, because "that's where the light is."... This book has tried to shed some light on some of the important detection challenges impeding future progress in clinical diagnostics. It may be the light is currently in the wrong place, but eventually the home keys will be found. Finally, we would like to thank the team at Royal Society of Chemistry who guided us so patiently through the publication maze and without whom there would be no book: Merlin Fox, Rosalind Searle and Alice Toby-Brant (Commissioning); Lois Bradnam and Sarah Salter (Production).

Pankaj Vadgama
London

Serban Peteu
Bucharest

List of Contributors

L. Max Almond Surgical Fellow, Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, United Kingdom

Dr. Salzitsa Anastasova Post Doctoral Research Assistant, School of Engineering and Material Sciences, Queen Mary University of London, Mile End Road, E14N, United Kingdom

Prof. Hugh Barr Professor of Surgery, Consultant General & Gastrointestinal Surgeon, Biophotonics Research Unit, Gloucestershire Hospitals NHS Foundation Trust, Great Western Road Gloucester GL1 3NN & Cranfield Health, Cranfield University, Cranfield MK43 0AL, United Kingdom

Dr. Christophe Blaszykowski Research Associate, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

Dr. Megan C. Frost Associate Professor, Department of Biomedical Engineering, Michigan Technological University, 1400 Townsend Dr., Houghton, MI 49931-1295, United States of America

Dr. Szilveszter Gáspár Senior Researcher, International Centre of Biodynamics, 1B Intrarea Portocalelor, 060101 Bucharest, Romania

Madeleine Hu Premed Student, the College of New Jersey, 2000 Pennington Road, Ewing Township, NJ 08628, USA, madeleinehu@yahoo.com

Dr. Joanne Hutchings National Institute for Health Research Post-Doctoral Researcher, Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, United Kingdom

Dr. Catherine Kendall Senior Lecturer, Biophotonics Research Unit, Gloucestershire Hospitals NHS Foundation Trust, Great Western Road Gloucester GL1 3NN & Honorary Senior Clinical Lecturer Cranfield Health, Cranfield University, Cranfield MK43 0AL, United Kingdom

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Prof. Naresh Magan Professor, Personal Chair, Applied Mycology, Research Director and Lead Academic for Doctoral Training Centre for Health and Biosciences, Cranfield Health, Vincent Building, Cranfield University, Cranfield MK43 0AL, United Kingdom

Dr. Christopher McNamara Consultant Haematologist, The Department of Haematology, Royal Free Hospital, London NW3 2QG, United Kingdom

Prof. Mark E. Meyerhoff Philip P. Elving Professor of Chemistry, Department of Chemistry, University of Michigan, 940 N. University, Ann Arbor, MI 49109-1055, United States of America

Dr. Serban F. Peteu Senior Scientist, National Institute for Research and Development in Chemistry and Petrochemistry, 202 Splaiul Independentei, 060021 Bucharest, Romania

Dr. Gavin Rhys-Lloyd Post-Doctoral Chemometrics, Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, United Kingdom

Dr. Alexander Romaschin Director, Clinical Biochemistry and Keenan Research Centre, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada

Prof. Wolfgang Schuhmann Professor, Analytische Chemie-Elektroanalytik & Sensorik, Ruhr-Universität Bochum, Universitätsstr. 150, Bochum D-44780, Germany

Sonia Sheikh Graduate Student, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

Prof. Neil Shepherd Professor of Histopathology, Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, Department of Histopathology, Gloucestershire Hospitals NHS Foundation Trust, Faculty of Bioscience and Medicine, Cranfield Health, Cranfield University, Bedfordshire, United Kingdom

Geeta Shetty Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, United Kingdom

Dr. Anna Spehar-Deleze Post Doctoral Research Assistant, School of Engineering and Material Sciences, Queen Mary University of London, Mile End Road, E14N, United Kingdom

Prof. Nicholas Stone Professor of Biomedical Imaging and Biosensing, Biophotonics Research Unit, Leadon House, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL13NN, United Kingdom, Biomedical Imaging and Bio Sensing, School of Physics, University of Exeter, EX4 4QL, United Kingdom

Prof. Sabine Szunerits Professor, Institut de Recherche Interdisciplinaire, Université Lille 1, Parc de la Haute Borne, 50 Avenue de Halley, BP 70478, 59658 Villeneuve d'Ascq, France

Dr. Alison S. Thomas Clinical Research Fellow, The Department of Haematology, The Royal Free Hospital, London NW3 2QG, United Kingdom

Prof. Michael Thompson Professor of Bioanalytical Chemistry, Department of Chemistry and Institute for Biomaterials and Biomedical Engineering University of Toronto, Canada

Prof. Pankaj Vadgama Director of the IRC in Biomedical Materials; Professor of Clinical Biochemistry, Queen Mary University of London, Mile End Road, London, E14N, United Kingdom; Consultant Chemical Pathologist in the Department of Clinical Biochemistry at Barts Health NHS Trust

Dr. Alina Vasilescu Senior Researcher, International Centre of Biodynamics, 1B Intrarea Portocalelor, 060101 Bucharest, Romania

Yuan Wang Senior Scientist, Siemens Healthcare Diagnostics, 511 Benedict Avenue, Tarrytown, New York, NY 10591, United States of America

Alexander K. Wolf Graduate Student, Department of Chemistry, University of Michigan, 940 N. University, Ann Arbor, MI 49109-1055, United States of America

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