EMRP Call 2011 - Health, SI Broader Scope & New Technologies

Selected Research Topic number: **SRT-h06**
Version: 1.0

Title: Metrology for the characterisation of biomolecular interfaces for diagnostic devices

Abstract

Molecular diagnostic devices are reliant on interface functionality to detect the presence, activity or concentration of target biomolecules such as disease biomarkers. However, current biotechnology lacks reliable, standardised metrology tools and methodologies for quantitative and direct characterisation of the interface. In order to provide a more reliable and efficient exploitation of molecular diagnostics technologies, traceable measurements through written standards and a complete characterisation of biomolecular interfaces is required. This should lead to an improvement in the sensitivity and reliability of diagnostic devices, increase their cost-effectiveness and provide high throughput quality control of them.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on “Grand Challenges” related to Health on pages 7 and 8 and in the sections on page 40 and 41.

Keywords

Molecular diagnostics, biomolecular interface, biomolecules, biosensor, surface analysis

Background to the Metrological Challenges

Improved characterisation of diagnostic devices is needed to support the regulatory requirements outlined in the European *in vitro* device (IVD) Directive 98/79/EC [1], which stipulates that analytical and diagnostic performance characteristics must be specified and guaranteed. The International Joint Committee for Traceability in Laboratory Medicine also supports the development of quantitative instead of only qualitative diagnostics.

To address this and overcome current challenges in characterising biomolecular interfaces, existing and novel methodologies need to be developed. Methods should give direct and quantifiable information on the sensors’ biomolecular layers and their interaction with target molecules and the surrounding media. Quantitative measurement and understanding of the molecular interface is also required, in terms of concentration of active functional groups, molecular orientation, surface coverage and homogeneity. In addition, the quality of the biomolecular interface is key for device behaviour in terms of sensitivity, specificity, reliability, reproducibility of assay results, product stability and shelf life.

The lack of validated measurement methods for diagnostic devices leads to poor reproducibility and control in their production, functionality and performance and is a significant barrier towards their use in commercial and clinical applications. Companies often adopt a trial and error approach to improve diagnostic performance because of a lack of expertise and reliable tools for detailed characterisation of interfaces. But, relying on expensive biological assays to test overall device performance does not provide sufficient information for product design and results in delayed product development and significant cost.

Despite the existence of common techniques, (e.g. scanning fluorescence microscopy) and more novel, quantitative surface analytical methods (e.g. X-ray photoelectron spectroscopy, secondary ion mass spectrometry, anomalous small-angle X-Ray scattering and near edge X-ray adsorption fine structure), these techniques have been rarely used to study biomolecular interfaces as they require validated methodologies and data interpretation. Techniques used to study molecular interfaces in aqueous media (e.g. surface plasmon resonance, ellipsometry, quartz crystal microbalance with dissipation, polarised fluorescence

measurements and novel scanning probe microscopy techniques) also need improvement in terms of their validity, standardisation and traceability. However, with improvement these methods could be used to characterise biomolecular interfaces and help diagnostic devices to meet European legislation.

Scientific and Technological Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

The JRP shall focus on the traceable measurement and characterisation of biomolecular interfaces to provide a more reliable and efficient exploitation of molecular diagnostics technologies.

The specific objectives are:

1. To develop quantitative and validated methodologies for the characterisation of diagnostic sensing interfaces. This may include:
    - Quantification of molecular composition, surface concentration and layer thickness,
    - Characterisation of orientation and binding mechanisms
    - Assessment of surface coverage and uniformity
2. To develop methodologies for characterising molecular biolayers by combining information from complementary techniques such as advanced optical techniques, mass spectrometry, X-ray spectroscopy and scanning probe microscopy.
3. To develop methodologies for evaluating the performance of sensing devices in biological media. This may include:
    - Quantifying the interaction of the sensing interface with plasma proteins and target molecules,
    - Measuring the interaction potentials and differentiation of specific and non-specific bindings.
4. To develop methodologies for the rapid and repeatable assessment of biomolecular interface quality, reproducibility and shelf life. This should be related to the current variability in diagnostic performance and current regulatory requirements.
5. To quantitatively and comparatively evaluate new and emerging approaches to biosensing (e.g. label-free approaches). This should include diagnostic sensitivity, specificity, reliability, potential for multiplexing, sensitivity to trace analytes and cost effectiveness.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this, including the currently funded EMRP project T3 J1.1. Nanoparticles; 'Traceable characterisation of Nanoparticles'.

The total eligible cost of any proposal received for this SRT is expected to be around the 2.7 M€ guideline for proposals in this call.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the “end user” community (eg letters of support) is encouraged.

You should detail other impacts of your proposed JRP as detailed in the document “Guide 4: Writing a Joint Research Project”

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the medical community.

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] *In vitro* device (IVD) Directive 98/79/EC