EMPIR Call 2017 – Industry, Fundamental, Normative and Research Potential

Selected Research Topic number: **SRT-i18**
Version: 1.0

Title: Translational metrology for synthetic biology and the manufacturing capability of the 4th industrial revolution

Abstract

The World Economic Forum in Davos introduced the concept of the 4th industrial revolution, in which Synthetic Biology was identified as the technology that will drive the world economy. However, in order to support the concept of the 4th industrial revolution the industrialisation of bio-manufacturing requires the development of accurate metrology for synthetic biology, including traceable reference standards, materials and methods. Such reference standards and methods must also be applicable for industrial use in terms of reliability and reproducibility and should address the inherent complexity of applied biology.

Keywords

Reference materials, Reference methods, Synthetic biology, 4th industrial revolution

Background to the Metrological Challenges

Bio-economy is increasingly a key factor in industrial growth driven by an expanding bio-manufacturing sector based on synthetic biology. Over the last decade technology has advanced systematic application of the reproducible principles of modularity, characterisation and standardisation to the engineering of biological systems and processes. Many of the major industries developed during the late 19th and 20th centuries use oil as a basic feedstock, coupled to the application of synthetic chemistry techniques. Oil and petrochemicals are non-sustainable, which has led to the concept of using a wide range of biologically-based feedstocks in order to enable synthetic biology to produce living cell-like systems for new processes and products; and hence supports the concept of the 4th industrial revolution.

Synthetic biology applies engineering principles to the design, building and testing of new biological systems at the primary component level (genetic, protein). The structural and functional properties of biological systems remain context-dependent and therefore, support the reproducibility of the bio-system and its successful implementation. However, in terms of the primary component level of biological systems, the development of reference standards is needed, as these are currently lacking across the full biological scale of parts for bio-manufacturing processes *in cellulo* and *in vitro* (cell-free systems).

Further to this, measurement standards for biological control elements are also needed to ensure reproducibility of manufacturing and engineering responses to external and internal variables used for auto-adaptive feedback production systems. For example, fluorescent reporters can be used to monitor output that can subsequently be applied to cell readings using flow cytometry. Such auto-adaptive feedback production systems could be used to standardise measurement protocols, thereby increasing measurement uniformity and comparability of data.

Currently, calibration and metrology standards describe the function of physical standards in absolute terms. However for these to be relevant to synthetic biologically (and made traceable to the SI), biologically relevant relationships and links to arbitrary measurement scales are needed. For example, protein expression can be defined in units of molecules per cell per unit time, but for measurement terms described in arbitrary units the best that can be obtained is a ratiometric measure, which leads to discontinuity in measurements and arbitrary assumptions in parameters required for modelling.

Finally, metrology for cell-free systems would support the construction of biological processes with predicted functionality, which could be implemented in living systems. There is a substantial demand from industry to develop the metrology needed for cell-free systems that functionally perform as live cells. Therefore such traceable measurement standards and artefacts for cell-free systems need to have their functionality demonstrated.

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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 protocol.

The JRP shall focus on the development of metrological capacity for synthetic biology and associated manufacturing capabilities.

The specific objectives are:

1. To develop and characterise validated and traceable reference materials across the biological scale of size and complexity to support the bio-manufacturing processes *in cellulo* and *in vitro* (i.e. cell-free systems).
2. To produce and validate traceable measurement methods and standards for biological control elements in order to ensure the reproducibility of manufacturing and engineering responses to external and internal variables necessary for auto-adaptive feedback production systems.
3. To develop SI traceable calibration standards and reference materials for synthetic biology. In addition, to demonstrate the use of such standards and materials for the calibration of arbitrary measurement scales, enabling transformation into absolute scales.
4. To develop and characterise traceable measurement standards and artefacts for cell-free systems and then demonstrate their functionality to perform as live cells.
5. To facilitate the take up of methods, technology and measurement infrastructure developed in the project by the standards developing and metrology organisations (e.g. CCQM Working Groups on Cell Analysis, Protein Analysis and Nucleic Acid Analysis, VAMAS Synthetic Biomaterials TWA40 and standards bodies associated with Directive 2007/1394/EC on Advanced Therapy Medicinal Products) and end-users (e.g. bio-manufacturing industries).

Proposers shall give priority to work that meets documented industrial needs and include measures to support transfer into industry by cooperation and by standardisation. An active involvement of industrial stakeholders is expected in order to align the project with their needs – both through project steering boards and participation in the research activities.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.5 M€, and has defined an upper limit of 1.8 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 30 % of the total EU Contribution to the project.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the bio-manufacturing sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. 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 EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.