European Partnership on Metrology
Call 2025 – Health, Integrated European Metrology, Regulation and Research Potential

Selected Research Topic number: **SRT-h14**
Version: 1.0

Title: Metrological framework for the practical use of luminescence thermometry in healthcare

Abstract

Precise and accurate measurement of temperature is critical in healthcare due to its influence on physical, chemical, and biochemical processes. Conventional thermometry is currently limited in measurements of cellular level transient temperatures that are needed for new therapies and diagnostics. Thermometry with luminescence thermometers (LTs) is capable of delivering high sensitivity, sub-micron resolution, in-situ monitoring and remote sensing, which are essential for organ to cell-scale thermometry in diagnosis and treatment. However, the integration of this method into routine clinical practice is still in the developmental stage. Challenges such as the need for precise calibration and the development of suitable delivery mechanisms together with general challenges of comparable luminescence measurements in biologically relevant spectral windows must be addressed prior to widespread adoption. Proposals are sought to address these challenges and to improve traceability and reliability of this thermometry approach for medical applications.

Keywords

Thermometry, luminescence, proton therapy, photonic sensors, nanoscale, phosphor thermometry, temperature traceability, biology, biological processes, cellular monitoring, nanothermometry, nanomedicine.

Background to the Metrological Challenges

Luminescence thermometry uses the temperature-dependent emission properties of luminescent materials such as changes in emission intensity and lifetime or spectral shifts, to measure local temperature and its changes with micrometre spatial resolution. This measurement method has emerged as a very promising tool for medical applications, due to its high sensitivity, high spatial and temporal resolution and suitability for non-contact and in-situ measurements. Luminescent thermometers can be constructed from multiple materials, for example, quantum dots such as Ag_2S, lanthanide-based nanoparticles, nanodiamonds and organic dyes, each offering tailored characteristics such as broad excitation spectra, spectrally fine-tuned emission spectra, and the required photostability for use as measurement medium. Luminescence nanothermometers, with emission in the diagnostically relevant long wavelength region such as rare-earth-doped nanoparticles, semiconductor nanocrystals and nanodiamonds, has seen remarkable progress over the last decades. Current cutting-edge developments include dual-mode luminescence thermometers that combine spectral and lifetime information for increased reliability and nanoscale spatial resolution. In addition, all luminescence thermometers can be combined with a targeting or recognition moiety to enable localised measurements on specific subcellular targets. This can provide a real-time mapping of localised underlying temperature gradients in tissues which could tackle diseases such as progressive neuronal dysfunction.

Recent advances led to the development of innovative temperature-sensing materials, resulting in a rapid expansion of the application of luminescence nanothermometry for precision medicine and advanced therapeutic strategies. This has highlighted the significant potential of luminescence thermometry for diagnosing medical conditions such as inflammation and strokes, and monitoring treatments such as hyperthermia tumour treatments.

Despite its great potential, the usage of luminescence thermometry in biological systems still has to overcome some challenges. For example, optical temperature measurement can not only be affected by temperature but also by environmental conditions such as pH or viscosity. In addition, luminescence measurements, especially

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in long wavelength regions > 1000 nm (short-wave infrared, SWIR) are challenging and suitable luminescence standards are not yet available to provide benchmark values. More importantly, the methods and luminescent thermometers developed by different groups lack comparability and standardisation. Further to this, achievable (material-specific) uncertainties have often not been evaluated, hindering the demonstration of clinical effectiveness. Addressing the metrological challenges of traceability, accuracy, reproducibility, and standardisation are crucial for transitioning these innovative techniques from experimental research into routine clinical and industrial applications.

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 proposal shall focus on the development of traceable and reliable measurement of cellular level transient temperatures using luminescence thermometry, to facilitate its effective use for medical research, accurate disease diagnosis and treatment in healthcare settings.

The specific objectives are

1. To develop reliable luminescence thermometry methods for measuring cellular level transient temperatures, with at least two bio-compatible luminescence thermometers used in biomedical research, therapy monitoring, treatment and diagnosis. To evaluate these methods and quantify (i) the main quantities influencing these methods including but not limited to environmental Ph and viscosity, (ii) the limits for their practical implementation, (iii) instrument-specific effects and signal affecting contributions, and (iv) the traceability of measurements using different wavelengths regions relevant for bio-medical research, diagnosis, therapy and treatments. In addition, to investigate the use of time-resolved spectroscopy for measuring sub-second temperature-induced changes.
2. To develop calibration procedures with the determination of uncertainty budgets of the methods from Objective 1 with a target standard calibration uncertainty value < 0.1 °C, for example by developing: (i) reference materials with known temperature-sensitive luminescence properties (ii) luminescence standards traceable to the spectral (photon) radiance scale and (iii) contact thermometers (micro-photonic sensors and/or resistance thermometers). The calibration procedures to be developed in biological conditions or mimicking biological environments (i.e., at different pH ranges, in the presence and absence of oxygen, and in the presence of proteins). Further to this, to develop metrologically advanced machine learning algorithms for the analysis of high-resolution luminescence thermometric data.
3. Using the outputs of Objectives 1 & 2, to develop validated, harmonised protocols for optical temperature measurement using temperature-sensitive luminophores. Then to produce a Good Practice Guide for clinicians, based on the use of the protocols. The developed good practice guide should take into account the inputs of relevant stakeholder from the medical field in order to create a document usable for the community outside metrology.
4. To conduct an interlaboratory comparison of luminescence thermometry, using the outputs of Objectives 1-3, including a variety of applications and wavelength regions relevant for bio-medical research, diagnosis, therapy and treatment.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (medical device manufacturers, calibration service providers, EURAMET TC-MC), standards developing organisations (e.g. IEC TC 113) and healthcare regulatory bodies (e.g. related to EU-IVDR and MDR), and end users (e.g. clinicians, medical researchers, pharmaceutical and microelectronics industries and other relevant stakeholders).

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, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development. Where relevant, proposals are encouraged to build on, or seek collaboration with, existing projects and develop synergies with other relevant European, national or regional initiatives and funding programmes. In particular, links are encouraged with (i) the projects funded under earlier relevant topics of the Horizon Europe programme; or (ii) other relevant European Partnerships.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this. In particular, proposers should outline the achievements of the Metrology Partnership project 23FUN01 PhoQuS-T and how their proposal will build on those.

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 2.1 M€ and has defined an upper limit of 2.6 M€ for this proposal.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated 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 proposal's 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,
- Facilitate improved industrial capability, or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the healthcare 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 the Metrology Partnership 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.

Timescale

The project should be of up to 3 years duration.