

Thermal and Infrared Biosensors for Biological Signal Detection

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Abstract: Thermal (infra-red) biosensors transform heat production, heat distribution, or the way infrared interacts with biological systems, into information about the system. These are wearable thermistors that track skin temperature, IR imaging that maps regional physiology, calorimetric devices that measure the reaction enthalpy, photothermal assays that convert optical absorption to a temperature increase and mid-infrared nanophotonic sensors that detect the molecular vibrational fingerprint. This review will discuss the principles, architectures, applications, and drawbacks of these platforms. Contact thermal sensors offer continuous measurements and can compensate biochemical signals for temperature; whereas non-contact thermography offers spatial maps of inflammation, perfusion, and fever-related pattern in a rapid fashion. Label free detection is possible with reaction-based thermal sensors, as almost all biochemical reactions involve heat exchange. Photothermal amplification enhances the point-of-care readout while surface-enhanced infrared absorption allows for chemically specific protein, lipid and nucleic acid analysis. Though laboratory performance is good, potential translation issues include environmental heat transfer, emissivity, motion, sample-matrix interference, small infrared absorption in the nanoscale, device-to-device variation, and limited clinical validation. Future systems that are most assured will integrate thermal or infrared signatures with complementary biochemical and physiological measurements, provide standardized calibration, integrate microfluidics, and have interpretable machine learning. Thermal and infrared sensing should be considered a family of biosensing technologies; that is, it should be approached as a family of technologies that facilitate a connection between physiological heat, molecular recognition, photonics, and data analytics.

Keywords: Bio inspecting using thermal biosensors, infrared thermography, photothermal biosensing, mid-infrared spectroscopy, wearable biosensor, meta surface

1. Introduction

A biosensor is composed of a biological process or recognition event and a signal that is biologically relevant and is linked to a transducer and an analytical output. Thermal and infrared methods are unique in being able to detect two types of information, related but different. The first is heat, that is, the metabolism, blood flow, inflammation, cellular growth and biochemical reactions change the temperature or heat flux. The second is the interaction with infrared radiation, or infrared absorption: biomolecules absorb infrared radiation at frequencies related to chemical bonds, and can be identified by their spectral signatures. In practice, contact temperature sensors, calorimetric biosensors, infrared thermography, photothermal assays, and infrared spectroscopic biosensors are included under the field.

The interest in such systems has increased due to the availability of a label-free and non-invasive system, ability to miniaturize the system, and the compatibility with continuous monitoring. For example, Gao et al. (2016) developed a wearable array to measure sweat metabolites and electrolytes along with skin temperature for sensor calibration. Subsequently, soft microfluidic platforms have been combined with sweat-rate and colorimetric biochemical measurements, as well as temperature (Choi et al., 2019). Infrared cameras can measure thousands of points of surface temperature at another scale without touching. Infrared spectroscopy is not efficient for detecting the vibrational fingerprints of thin biomolecular layers, but this is possible with nanophotonic sensors (Rodrigo et al., 2015).

It's a very significant word, signature. It is not usual for there to be only one temperature value that is specific to one biological condition. A diagnostic signature is typically a temporal, spatial, wave length or multi-spectral signature. The aim of this paper is to summarize the way these thermal and infrared signatures are acquired by biosensors, discuss the primary platforms, review applications, and discuss the requirements to reliably translate the signature.

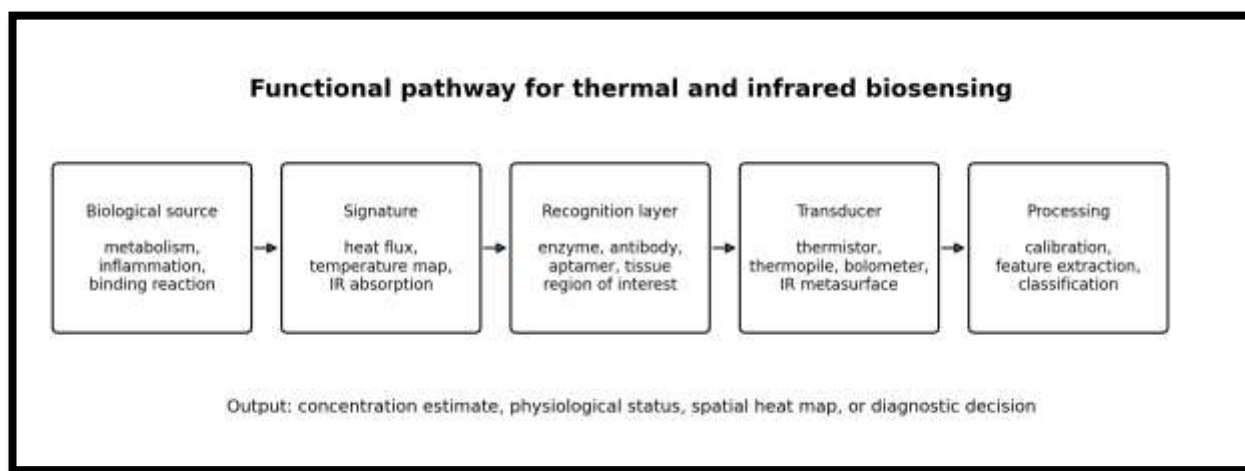


Figure 1: Functional pathway for thermal and infrared biosensing.

2. Review Method

The narrative-review approach with a focus is applied in this paper. Studies were chosen to represent four main categories: wearable or contact thermal sensors, non-contact infrared thermal imaging, reaction-based calorimetric and photothermal sensing, and mid-infrared molecular biosensors. Researches with a fully described sensing pathway from a biological event to measurable output were given priority as were those that included discussions of calibration or validation. Clinical and engineering reviews were added to the basic reports. There is no new clinical data or meta-analysis presented, only a synthesis. Published ideas are arranged in the table and figures, and the emission graph is an original calculation, based on Planck's radiation law.

3. Basics of thermal and infra-red signatures

Any human tissue that is warmer than its surroundings radiate electromagnetic energy. Most of the measurement possible is in the long wave infrared band and makes 8-14 μm cameras useful in thermal imaging at typical skin temperatures. As seen in Figure 2, slight temperature variations have significant effects on the radiance of the spectrum. But an infrared camera doesn't directly measure core temperature. The apparent signal can vary due to convection, evaporation, ambient temperature, humidity, viewing angle, cosmetics, clothing, and recent activities. Standardized acquisition and blackbody-based calibration are thus critical (Ghassemi et al., 2018; Usamentiaga et al., 2014).

The principle of molecular infrared sensing is different. Radiation is absorbed by chemical bonds at certain frequencies. Amide bands are prominent in proteins, hydrocarbon and carbonyl vibrations are seen in lipids, and phosphate and base-related features are seen in nucleic acids. These signatures can indicate composition and/or conformation. The issue is

sensitivity; the wavelength of infrared radiation is many times larger than the nanoscale biomolecular layers, and there is strong absorption by water. Effective techniques for increasing the intensity of the electromagnetic field in the immediate vicinity of the trapped molecules and the intensity of their response include plasmonic nanoantennas, graphene resonators, metasurfaces, microfluidic control and surface-enhanced infrared absorption (Etezadi et al., 2017; Rodrigo et al., 2015).

Thermal reaction sensing is in the middle. Heat is either liberated or consumed during enzyme-substrate binding, oxidation, hybridization and catalytic reaction. With a differential thermistor or microcalorimeter, the difference between an active chamber and a reference chamber is used to eliminate common temperature drift. The method is label-free, as heat is a universal reaction product, but selectivity will need to be achieved by the recognition chemistry.

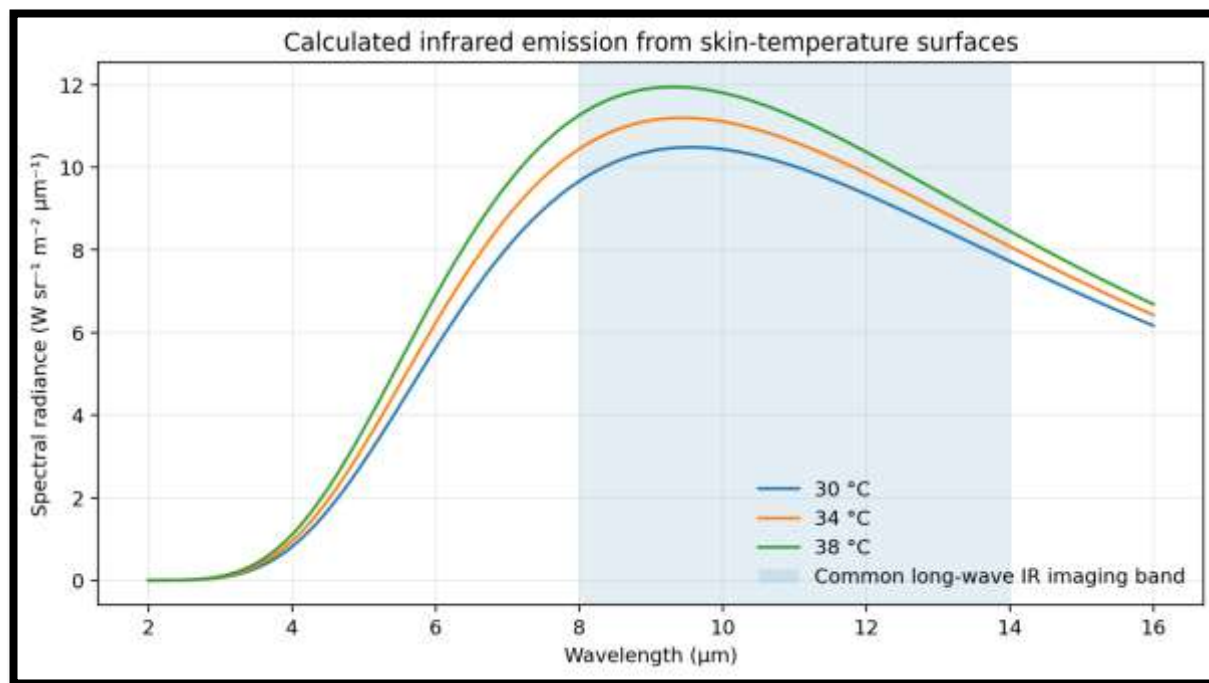


Figure 2: Calculated blackbody spectral radiance for surfaces at 30 °C, 34 °C, and 38 °C. Curves were generated from Planck's law; the shaded region indicates the common long-wave infrared imaging band.

4. Major Biosensor Platforms

The contact thermal sensors are typically made of thermistors, resistance-temperature detectors, thermocouples, semiconductor junctions or composite materials. They have advantages of continuous sampling, small power consumption and convenient integration with wearable electronics. They suffer from thermal lag, non-uniform skin contact, artifacts caused by strain, a small temperature difference between skin and body, and sensor self-heating. Enzymes are also influenced by temperature, as are electrode potentials and diffusion; thus, it is likely that the most important application of temperature in a multiplexed wearable is both as a physiological variable and as a correction variable. This dual function was demonstrated by Gao et al. (2016) and the combination of epidermal microfluidics and local temperature and sweat chemistry was demonstrated by Choi et al. (2019).

Infrared thermography is the process of making a 2D image of the temperature by using a detector array. It is quick, non-contact and can be used for repeated measure. Pauk et al. (2019) reported that hand thermography could help evaluate the activity of rheumatoid-arthritis due to the inflammatory and vascular processes affecting regional heat distribution. Diabetic-foot monitoring, wound assessment, vascular disorders and fever screening are among the other applications of thermography that have been investigated. But fever screening is one example of the specificity challenge. The wide variation in performance has been reported by Khaksari et al. (2021) as the surface temperature of the face is not an ideal proxy of core temperature and as the symptoms of asymptomatic infections are not necessarily associated with fever. Sun et al. (2017) developed a multifaceted system that provided estimation of multiple vital signs

from combined visible and thermal imaging to show that this combination has an improved screening performance over using only temperature.

Calorimetric biosensors measure the heat of recognition or catalytic reactions. Vermeir et al. (2007) designed a differential microplate calorimeter biosensor that could quantify ascorbic acid in a small sample volume using an ascorbate-oxidase reaction. The platform demonstrates three design principles: immobilized recognition element, matched reference and thermal isolation. Calorimetry is widely used with metabolites, enzymes, microbes, and cell activity, but requires low noise instrumentation and the flow and drift of the baseline must be carefully monitored.

In the case of photothermal biosensors, the thermal output is intentionally increased. The analytical signal is the temperature rise when a light-absorbing label or reaction product absorbs the light. To quantitatively detect pathogens' DNA, Zhou et al. (2020) employed an 808-nm source, gold-nanoparticle-assisted chemistry, paper microfluidics and a low-cost thermometer. These assays can be more accurate than visual color reading in highly colored samples and can be implemented with low-cost electronic devices. Four additional safety, laser alignment, heat loss, and nanoparticle reproducibility are important considerations.

Chemical specificity is sought after by mid-infrared biosensors instead of temperature only. Rodrigo et al. (2015) used graphene plasmons to access protein monolayers at specific molecular vibrations using electric tuning. In the same fashion, the formation of lipid membranes was demonstrated in real time and without tags using infrared nanoantennas by Limaj et al. (2016). Etezadi et al. (2017) distinguished between protein secondary-structure states via nanoplasmonic arrays. Hui et al. (2021) created tetrahedral DNA nanostructure (T4 DNA) with a surface-enhanced infrared absorber (SEIR) for the detection of miR-155. Recently, Kavungal et al. (2023) integrated an immunoassay, an infrared metasurface, microfluidics, and an artificial neural network to distinguish the structural forms of alpha-synuclein. The results of these studies demonstrate the development of bulk refractive-index change detection to chemically and structurally informative spectra.

5. Applications and Comparative Value

Longitudinal monitoring is the most important biomedical use of contact thermal sensing. One measurement of a given Trend may be more useful than a single measurement, during exercise, sleep, infection, menstrual cycling, recovery, or wound healing. Wearable temperature channels also enhance the interpretation of sweat and electrochemical sensors as reaction and electrode responses are temperature-sensitive. Microthermal sensors could monitor implant inflammatory responses, local perfusion, cellular proliferation or treatment responses in implants or cell-culture systems.

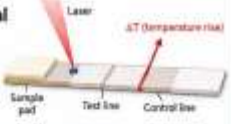
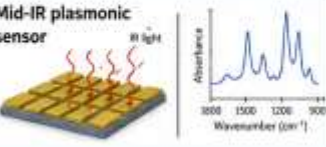
Thermography works best for spatial questions, such as: is one side warmer than the other side, is the margin of a wound getting bad perfusion, is the inflammation following a pattern of the body. The attractive properties are that it is contactless and radiation free and is suitable for triage and repeated follow-up. However, it should typically not be used as a separate diagnostic test.

When a label-free, low cost, or instrument-light assay is needed, calorimetric and photo-thermal methods can be employed. They can be modified for the purposes of food safety, pathogen detection, environmental monitoring, enzymatic analysis and point-of-care diagnostics. A second need is label-free identification and structural characterization, which is served by molecular platforms utilizing infrared spectroscopy. They could be useful for early disease research and therapeutic monitoring, as they are able to distinguish protein conformation, membrane processes and nucleic-acid targets. These modalities are compared in table 1 and we stress that not one of these platforms is ideal for all of these four characteristics of spatial coverage, molecular specificity, portability, and clinical simplicity.

Table 1: Comparison of thermal and infrared biosensor platforms

Platform	Measured signature	Typical application	Principal strength	Key limitation
Wearable contact sensor	Local temperature or heat flux	Continuous physiology; correction of sweat sensors	Compact and continuous	Contact, motion, and ambient effects
Infrared thermography	Spatial surface-temperature map	Inflammation, perfusion, wounds, fever triage	Non-contact and wide-area	Low disease specificity; environmental sensitivity
Calorimetric biosensor	Reaction enthalpy	Metabolites, enzymes, cells, food analysis	Universal label-free transduction	Very small signals and baseline drift
Photothermal assay	Light-induced temperature rise	Nucleic acids, pathogens, lateral-flow amplification	Low-cost quantitative readout	Optical interference and heat-loss variability
Mid-IR plasmonic sensor	Molecular vibrational absorption	Proteins, lipids, nucleic acids, conformational states	Chemical and structural specificity	Water absorption and nanofabrication complexity

Note. Categories overlap: for example, a photothermal assay may use an infrared source, and wearable systems may integrate biochemical recognition with temperature compensation.

Visualization/ Comparison of Thermal and Infrared Biosensor Platforms				
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6. Performance Requirement and Limits.

There need to be reliable systems to differentiate between biological and measurement variation. In the case of contact sensors, such criteria as accuracy, resolution, response time, hysteresis, drift, mechanical stability, biocompatibility, and calibration following repeated bending or sweating of the contact sensor are typically relevant. In the case of thermal cameras, spatial resolution, noise-equivalent temperature difference, emissivity setting, uniformity, working distance, choice of facial region or anatomical region, and environmental stabilization will be of concern. The need of standardized testing is due to the fact that software processing can significantly alter the temperature reported (Ghassemi et al., 2018).

Analytical biosensors also need selectivity, limit of detection, dynamic range, recovery, reproducibility and inability to be affected by complex sample matrices. Nspecific mixing heat and ambient drift may be higher than the target signal in calorimetry. Unrelated optical absorption in an assay can lead to a false increase in photothermal assays. Mid-infrared sensing has water absorption, surface foulage, resonance fabrication tolerances and spectral overlap making analysis difficult.

Technical sensitivity is different to clinical validity. Even a clear thermal pattern can not be disease specific since an inflammation, exercise, medication, stress and environment can have features similar to one. Machine-learning results may be stronger than they seem due to data imbalance and site biased acquisition. Prerequisites to diagnostic use are external validation, blinded testing, transparent preprocessing, uncertainty reporting and comparison to accepted reference methods. Confidentiality is also an issue since mystery thermal traces and physiological patterns are capable of illustrating vulnerable health and conduct.

7. Design and Validation Framework.

Developable pathway A defensible development pathway starts with defining the intended use. A tool to track the developments on a single patient will not need the same details as a population-screening tool or a molecular diagnostic test. Before choosing a transducer, developers should provide the anticipated signal magnitude, decision threshold, target biological event, anatomy or sample location, and the operating environment of the device, and how their device is to be utilized in reference mode. This avoids the usual trap of maximising sensitivity without demonstrating that the measured signature, answers a clinically or biologically important question.

The whole measurement chain should then be tested by analytical validation. Contact sensors need to be compared to traceable thermometry over the targeted temperature scope, evaluations during bending and motion, multiple attachment trials, and response evaluations under sweat and varying airflow. A thermography protocol must regulate the acclimatisation period, the distance between the camera and the subject, and the viewing angle, background radiation, emissivity, room temperature, humidity, and whether an external temperature reference is being used. The fixation of regions of interest and image-processing steps must be fixed prior to outcome analysis. Assays based on reaction require blank, non-specific, and matrix controls whereas infrared molecular sensors demand reference spectra, surface-regeneration experiments, and inert biofluid measurements.

Biological validation is the next step. The degree of measurements is supposed to be compared with accepted clinical, microbiological, biochemical, or spectroscopic measurements. Repeats of a participant and reproduction across operators, days, instruments and sites will have to be reported independently. The research design should incorporate healthy variation and realistic confounders as opposed to just having clear, positive, and negative samples. In the case of algorithms, the participant should be separated into training, validation and external test set. Accuracy is less informative because there are more informative tools such as calibration plots, sensitivity, specificity, predictive values, uncertainty intervals, and failure rates.

Lastly, usability and outcome evaluation can be used to ascertain the practical value of the technology. An item(wearable) should be comfortable and stable when performing realistic activity; a thermal camera workflow should be speedy enough to serve the desired environment and an infrared molecular instrument should have practicable sample preparation. Future research is needed that involves testing that information provided by the biosensor alters a choice, diagnoses faster, unnecessary testing is minimized or monitoring is enhanced. This artificial structure to which the

engineering work is tied to the biological validity and minimizes the chances of falsely turning a prospective laboratory signature into a convenient diagnostic instrument.

8. Future Directions

Multimodal thermal and infrared biosensors of the future are probable. Fusion can be done between temperature, heat flux, heart rate, respiration, biochemical markers, and infrared spectra to eliminate sources of ambiguity. Continuous sampling will be enhanced with the implementation of flexible electronics and microfluidics, whereas on-device processing will help reduce the transmission of data and protect privacy. Metasurfaces and tunable graphene could be used to implement compact infrared spectrometers, and photothermal conversion could be used to read instrument-light in resource constrained systems.

Machine learning is practical when the signatures are multi-dimensional, yet the models must be guided by physics and be tested in the population, devices and settings. Individual baselines can also be effective: an anomaly of single person thermal distribution can be of greater importance than the comparison to a single population threshold. The manufacturing of translation will also demand stable surface chemistry, reference standards and prospective studies, which will show that the sensor enhances a decision or result as opposed to the generation of more data. In other fields of application, assessment of food-quality, growth of microorganisms, environmental toxicology, animal health and control of bioprocesses can be assisted with the use of the same design principles. Thermal signatures can be used in such environments to detect fermentation, contamination, stress, or enzyme action, and infrared spectra can be used to detect chemical composition in the absence of fluorescent labels. A disposable recognition cartridge could be used with a reusable thermal or infrared reader in a portable system. These modular designs would reduce the price, ease quality control and enable one detector to be used in a variety of assays. The general opportunity is thus a platform model whereby selective biology is manipulated on the sensing surface and calibrated thermal, photothermal or infrared equipment is kept constant.

9. Conclusion

Thermal and infrared signature sensors range over a number of complementary technologies. Continuous local sensor (wearable temperature sensor) is used to improve biochemical-sensor calibration and provide continuous information in real time. Infrared thermography provides fast spatial heat maps of physiological heat. Calorimetric and photothermal biosensors will change biochemical reactions into temperature changes, and nanophotonic mid-infrared sensors will measure molecular composition and structure by vibrational fingerprinting. They both have the advantage of enabling the generation of label-free or minimally invasive data, although they are susceptible to heat transfer, environmental variability, spectral interference, and non-specific relationships with biology. The most powerful systems will involve standardized acquisition, selective recognition chemistry, various sensing modalities and clinically appropriate interpretation. Contextual patterns of thermal and infrared signatures can hence form potent part of accuracy monitoring and diagnostics when they are considered as pattern and not an individual temperature reading.

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