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REVIEW ARTICLE

Thermometry and interpretation of body temperature

Wenxi Chen[1]

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Abstract
This article reviews the historical development and up-to-date state of thermometric technologies for measuring human body temperature (BT) from two aspects: measurement methodology and significance interpretation. Since the first systematic and comprehensive study on BT and its relation to human diseases was conducted by Wunderlich in the late 19th century, BT has served as one of the most fundamental vital signs for clinical diagnosis and daily healthcare. The physiological implication of BT set point and thermoregulatory mechanisms are briefly outlined. Influential determinants of BT measurement are investigated thoroughly. Three types of BT measurement, i.e., core body temperature, surface body temperature and basal body temperature, are categorized according to its measurement position and activity level. With the comparison of temperature measurement in industrial fields, specialties in technological and biological aspects in BT measurement are mentioned. Methodologies used in BT measurement are grouped into instrumental methods and mathematical methods. Instrumental methods utilize results of BT measurements directly from temperature-sensitive transducers and electronic instrumentations by the combination of actual and predictive measurement, invasive and noninvasive measurement. Mathematical methods use several numerical models, such as multiple regression model, autoregressive model, thermoregulatory mechanism-based model and the Kalman filter-based method to estimate BT indirectly from some relevant vital signs and environmental factors. Thermometry modalities are summarized on the dichotomies into invasive and noninvasive, contact and noncontact, direct and indirect, free and restrained, 1-D and n-D. Comprehensive interpretation of BT has an equal importance as the measurement of BT. Two modes to apply BT are classified into real-time applications and long-term applications. With rapid advancement in IoT infrastructure, big data analytics and AI platforms, prospects for future development in thermometry and interpretation of BT are discussed.

Keywords Body temperature · Thermometry · Thermometer · Body temperature measurement · Body temperature interpretation · Body temperature analysis

1 Introduction

A 70-kg human body is estimated to consist of 37.2 trillion cells on average [1]. Many kinds of organelles are scattered throughout the plasma within living cells and are enclosed by cell membranes. Organelles are highly active and constantly communicate with each other through membrane contacts. Interorganelle communication plays an indispensable role in regulating biochemical processes and is essential for cell function and organism homeostasis. Mitochondria are one of the most important organelles. Various biochemical processes happen in mitochondria where microchemical factories work for the synthesis and decomposition of complex chemical reactants autonomously and rhythmically. Proper retention and timely regulation of temperature and pressure are required for these biochemical processes to secure metabolic activities for body functions and appropriate reaction to endogenous and exogenous stimulants.

In clinical settings, four principal vital signs, i.e., heart rate (HR), body temperature (BT), blood pressure (BP) and breathing rate (BR), are routinely measured as indicators for evaluating fundamental body functionality and efficiency.

The first comprehensive study on BT and its relation to human diseases was conducted by Carl Reinhold August Wunderlich in the late 19th century. He asserted that BT measurement "is a part of our method of diagnosis or

✉ Wenxi Chen
wenxi@u-aizu.ac.jp

[1] Biomedical Information Technology Laboratory, Research Center for Advanced Information Science and Technology, The University of Aizu, Aizu-Wakamatsu, Fukushima, Japan

observation of disease which is indispensable in all the cases where the temperature varies, very useful in many doubtful cases, and an auxiliary in almost every case." [2]

1.1 The essence of temperature and body temperature

Constant internal vibrational and rotational motions in molecules generate heat, or thermal energy. Total thermal energy depends on the type and mass of molecules in a substance. Temperature is a measure of the average thermal energy of molecular motions independent of a substance's properties.

Just as many chemical reactions are temperature-dependent, biochemical processes take place inside living cells and are greatly influenced by BT. These biochemical processes are collectively referred to as metabolism, and are divided into catabolic and anabolic metabolism. Catabolic metabolism is an exothermic reaction that disassembles larger molecules into smaller ones, such as breaking down a glucose molecule into two pyruvate molecules while storing energy as adenosine triphosphate (ATP) and reduced nicotinamide adenine dinucleotide (NADH) released during this biochemical process. Anabolic metabolism is an endothermic reaction that congregates smaller molecules into larger ones, such as joining amino acids to form a protein.

The human body is homeothermic, which maintains its temperature at a certain level to coordinate its metabolic activities by its inherent thermoregulatory mechanisms. BT indicates a human body's average thermal energy generated by metabolism within the body.

Wunderlich stated "Deviations from the normal course of temperature are certainly to be regarded as significant, and as never occurring without due cause… The discovery of abnormal temperatures in men who have previously exhibited a normal degree of heat is, therefore, a means of discovering or confirming the existence of latent disease." [2]

The normal BT (normothermia) is a basic prerequisite for proper body functions. Abnormal BT may be either hyperthermia (too high) or hypothermia (too low), and both temperature statuses can alter metabolic activities, perturb organic function and cause tissue damage. Even small variations can cause significant body function changes. An increased BT leads to a large decrease in mental and physical performance. On the other hand, a decreased BT can lead to impaired consciousness or in extreme cases to circulatory collapse.

1.2 BT set point and thermoregulatory mechanisms

Retaining the BT within a proper range has an important physiological significance. The normal BT was statistically investigated by Wunderlich through collecting several million observations obtained from some 25,000 subjects since 1861 using a mercury thermometer measured in the armpit. It was estimated that the average normal axillary BT value is 37.0 °C, and normally ranges between 36.2 and 37.5 °C [3].

The thermoregulatory mechanisms play important roles in maintaining physiological homeostasis. There is a thermoregulatory center in the hypothalamus responsible for regulating heat gain and loss to maintain BT at a reference set point within a limited range for a body to function properly whenever the exterior and interior environments change.

The set point is regulated and stabilized primarily by the anterior hypothalamic nucleus and the adjacent hypothalamic preoptic region. As their temperature deviates from the default set point due to various stimulants, thermoreceptors transduce these stimuli into neural impulses, and the endocrine system initiates to increase or decrease energy production or dissipation to return the temperature toward the set point.

The stimulants include proprioception, exteroception and interoception. Thermoreceptors such as cutaneous sensory receptors are exteroceptors for receiving thermal stimuli of hot and cold. They are terminal branches of thin myelinated A_δ and unmyelinated C fibers. A_δ fibers are cold receptors and activated at around 10–35 °C. C fibers are hot receptors and activated at around 35–45 °C.

Although surface body temperature can be tolerated in a broad range and reach close to 0 °C in an extreme condition, the core body temperature is still maintained at the rational physiological set point around 37.0 °C by the thermoregulatory mechanisms.

In a hot environment, vasodilation increases blood flow of arterioles through the arteries, and redirects blood into the superficial capillaries beneath the skin to accelerate heat loss by convection and conduction. Sweating is a responsive way to lose heat by evaporating water through eccrine sweat glands under the skin toward the skin surface.

In a cold environment, vasoconstriction leads to arterioles' contraction and less blood flows to superficial capillaries under the skin, more blood will return from the skin to the core of the body, and therefore prevents blood from losing more heat to the surroundings through the skin surface. In addition, other effective responsive exothermic mechanisms are also activated to maintain a stable core temperature. Besides muscle shivering and sweat suppression, the nonshivering thermogenin protein (uncoupling protein 1, or UCP1) in the mitochondria of brown adipose tissue will be metabolized and produce heat to increase the core temperature.

Still, no evidence at the molecular level has been found yet to indicate what genes are involved in determining the set point in the thermoregulatory mechanisms. Hypothalamus stimulants are produced by comparing central and peripheral temperatures and processing other vital sign information to

activate the thermoregulatory mechanisms that seem to be adaptive processes computationally and nongenetically [4].

1.3 Impact factors on BT

There are many factors impacting BT measurement. A measured BT value depends not only on physiological aspects such as pathological incidents and health condition but also anthropological attributes and measurement settings [5, 6].

In physiological aspects, hyperthermia occurs due to the body producing or absorbing more heat than it can dissipate when it suffers from inflammatory diseases, or exposures to a high-temperature environment for a long time. The thermoregulatory mechanisms are unable to deal with the heat, and eventually cause the BT to increase. Hyperthermia commonly leads to headache, confusion, fatigue, dehydration, and finally life-threatening.

In contrast, hypothermia happens due to excessive exposure to a cold temperature environment when the body loses heat more quickly than it can produce heat. Subjects suffering from mental illnesses and dementia may lack a sensation of cold, and tend to stay outside in cold temperatures too long. Alcohol or drug abuse can also impair judgment capacity about the cold. Some pathological conditions, such as hypothyroidism, arthritis, dehydration, diabetes and Parkinson's disease, can affect the human ability to maintain a stable core body temperature or to sense cold stimuli.

Anthropological attributes include age, gender, body weight, height, psychological status, biorhythmic phase and menstrual cycle stage in females. Measurement settings include physical activity level (waking or sleeping, resting or exercising), food intake and measurement modality, measurement time of day, measurement position and environmental factors.

1.4 Types of BT

BT ranges widely depending on various physiological and metrological factors as mentioned above. Many positions are available for BT measurements, such as sublingual, axilla, groin, neck, rectum, vagina, esophagus, tympanum, external auditory canal, nasal cavity, bladder, digestive tract, thorax and forehead. Normothermia BT values measured sublingually range from 33.2 to 38.2 °C [7]. Moreover, BT can also be measured at any time of the day, the difference between maximum and minimum in a day for a healthy subject may reach about 1.0 °C [6].

In practice, three types of BT measurement, core body temperature (CBT), surface body temperature (SBT) and basal body temperature (BBT), are commonly used according to its measurement position and activity level.

To evaluate the physiological default set point of BT for the body functions properly, CBT is preferred. CBT denotes the BT measured in deep positions of a body and is considered the operating temperature of all inner organs inside the body, specifically in deep structures of the body such as the brain, the heart and the liver, that are the closest BT as representative surrogate for the physiological set point of BT, in comparison to temperatures of peripheral tissues. CBT is normally maintained within a narrow range so that essential metabolic reactions can occur properly, the body functions can be optimized efficiently. Significant CBT elevation (hyperthermia) or depression (hypothermia) may lead to body malfunction.

The BTs measured on the positions such as rectum, esophagus, digestive tract, nasopharynx, bladder, uterus and aortic arch via invasive means such as a needle-type or a catheter-type are widely accepted as measurements of CBT. Although the aortic arch BT is generally considered to be the most accurate readings for CBT physiologically, CBT measured in the rectum is used as the gold standard of CBT clinically.

Besides CBT, by considering the measurement site, SBT is the value measured in sublingual, axilla, groin, neck, ear (tympanum, external auditory canal), thorax, forehead and elsewhere on the body surface. SBT is easy to measure noninvasively but is susceptible to environmental factors. For example, poor contact between the body surface and the thermometer may lead to measurement artifacts. Hot or cold drinks and respiratory flow may affect oral BT measurement. SBT is usually lower than CBT. When measuring sublingual BT and rectal BT simultaneously on a subject, the former BT is approximately 0.5 °C lower than the latter.

By considering the activity level when the body is in the most restful state with the lowest metabolic rate (usually during sleep), the measured BT values are defined specifically as BBT, which is commonly used to evaluate the menstrual cycle in females. Prior to a fully automatic continuous BT thermometer being available, practical BBT was conventionally measured sublingually in the morning right after awakening from sleep and before any physical activity has been undertaken, although the temperature measured at this time is somewhat higher than the true BBT.

2 Thermometry of BT

Ancient physicians used their hands to sense the BT by touching a subject as shown in Fig. 1. BT was used as one of the oldest barometers not only for diagnosis of human illnesses but also in promotion of daily healthcare. An ancient medical book "Pulseology," which was estimated compiled before BC 168 and excavated in 1973, Changsha City, China, contained an explanatory note on a pithy proverb, "keeping head cool and feet warm," and told us how to achieve better sleep [8, 9].

Fig. 1 Archaic method for diagnosis of disease using the body temperature difference between head and foot by touching a subject

Since the connection between temperature and the expansion of materials had been recognized, one of the earliest instruments to measure temperature was a glass flask that was partially submerged in water, and its upward or downward movement depended on the temperature changes. Many materials, such as alcohol, mercury and gallium, were also used later to measure temperature.

To measure temperature quantitatively, one of the early temperature scales was developed in 1701 by Ole Christensen Rømer to quantify the temperature between two fixed points at which water boils and freezes [10].

The Fahrenheit scale was established by Gabriel Daniel Fahrenheit in 1724, which divided the temperature range between the melting and boiling points of water into 180 equal intervals as degree Fahrenheit (°F). The Celsius scale was invented in 1742 by Anders Celsius who divided the range of temperature between the freezing and boiling temperatures of water into 100 equal divisions as degree Celsius (°C). The Kelvin scale (K) was devised by William Thompson Kelvin in 1848, which extended the Celsius scale down to absolute zero, a temperature level at which there is a complete absence of heat energy.

These three kinds of temperature scales became the metrological basis for modern thermometry. Although both the Fahrenheit scale and the Celsius scale are used in BT measurement, the former is used mainly in the United States, and the latter is used in most other countries.

To date, numerous methodologies based on heat energy transfer mechanisms such as radiation, conduction and convection have been developed. Many temperature-dependent properties such as acoustic velocity and resonance, electrical impedance, chemical reaction and metallic conductivity were utilized to measure temperature in diverse industrial fields by various methods underlying the wide diversity of chemical and physical principles, such as thermography, evaporography, spectroscopy and optical interferometry.

With a comparison of industrial measurements, two special aspects in BT measurement should be mentioned. Technologically, BT measurement is in the lower range of temperature but requires higher resolution, faster response, better repeatability and stability, better affinity and minimum disturbance to human organs, tissues and physiological conditions. Biologically, on the other side of severe technical requirements, interweaving among multiple vital signs and interactive causality with environmental factors accommodated by thermoregulatory mechanisms provide rich informative options for us to measure BT via other alternative ways. Two categories of methodology are introduced into BT measurement: instrumental methods (direct measurement of BT) and mathematical methods (indirect measurement of BT).

2.1 Instrumental methods

Instrumental methods utilize the results of BT measurements directly. Heat energy is transferable via three approaches: convection, conduction and radiation. These phenomena are utilized to devise various thermometers based on their physical and chemical principles in converting heat energy to a temperature reading. There are two main parts, transducer and instrumentation, in this kind of thermometry. A transducer converts heat energy or temperature into other forms of energy. An instrument processes the converted quantity to make it visible and legible on a temperature scale.

2.1.1 Transducers

Any substance with a temperature-dependent property, such as volume, density, resistivity and velocity, can serve as a transducer for temperature measurement.

Water was used as a transducer to measure temperature variations based on its property of thermal expansion and contraction in volume by Galileo Galilei for the first time in 1593. He used a container filled with bulbs of varying mass of water, each with a temperature marking. Because the buoyancy of water changes with temperature, some of the bulbs sink while others float, the lowest bulb indicates the current temperature. Alcohol was enclosed in a glass tube as the sensing liquid in place of water by the Grand Duke of Tuscany, Ferdinand II in 1654. However, neither of them was accurate enough. Liquid mercury was used as the temperature-sensitive transducer by Daniel Gabriel Fahrenheit in 1714. He also devised the Fahrenheit scale in 1724 to describe accurate temperature reading, which defined 180 degrees between the freezing and boiling points of water. The freezing point was 32 °F and the boiling point was 212 °F [11].

Besides the above liquids, many metals, such as platinum, nickel, aluminum and tungsten are also subject to

temperature change, their resistivity increases with increasing temperature.

A resistance temperature transducer (RTT) consists of a length of fine wire wrapped around a ceramic or glass core. The RTT wire is a pure metal, typically platinum, nickel or copper. These metals have an accurate relationship between resistance and temperature [12]. Their temperature coefficient (K^{-1}) is of order 10^{-3}, resistivity (Ω m) is of order 10^{-8}.

For example, copper has an approximately linear relationship between resistance and temperature over a wide range of temperatures.

$$R(T) = R_0\left(1 + \alpha\left(T - T_0\right)\right),$$

where, R_0 is the resistance of the metal at a known temperature T_0; R is the resistance at T which is the temperature to be measured; $\alpha = \frac{1}{R}\frac{dR}{dT}$ is the temperature coefficient of the metal.

In contrast, tungsten demonstrates the power relationship below:

$$R(T) = R_0\left(T/T_0\right)^{\mu},$$

RTTs have higher accuracy and repeatability, and are commonly used in temperature measurement below 600 °C.

A thermistor is a semiconductor–resistive temperature transducer made from sintered oxides of metals such as manganese, cobalt, nickel, iron or copper. It can be two to four mixtures and molded into various shapes at 1200–1500 °C.

The resistivity ρ of a thermistor at temperature T is expressed as

$$\rho \propto e^{\frac{E_g}{2kT}},$$

where, E_g is the band gap energy of the semiconductor, k is the Boltzmann constant.

A thermistor is suitable for BT measurement where relatively higher resolution is required in a narrow temperature range.

Thermistors have significant features such as high sensitivity (−2.8 to −5.1%/°C), easy fabrication and miniaturization in various shapes, selectable wide range of resistance values (tens Ω to hundreds kΩ) and wide measurement range (−50 to 350 °C).

Compared with a pure metal like platinum as the temperature transducer, which has a temperature coefficient of about 0.0039/K, the temperature coefficient of a thermistor can be either negative (negative temperature coefficient, NTC) or positive (positive temperature coefficient, PTC). An NTC thermistor has an inverse proportional relationship between temperature and resistance, typically about −0.04/K, i.e., the sensitivity is about 10 times that of a platinum sensor. NTC is commonly used in BT measurement because it has a good linearity in the physiological range of BT. A PTC has a positive proportional relationship but poor sensitivity in the BT range only suitable for higher temperature measurement (above 80 °C).

A PN junction can also be used as a temperature transducer. The forward voltage drop across a forward-conducting PN junction of a diode or transistor at constant forward-bias current exhibits excellent linear temperature dependence over a wide temperature range. The sensitivity between the voltage variation and temperature change is approximately 2 mV/°C, being virtually linear over the range of −40 to +100 °C [13, 14]. The high resolution of at least ±0.01 °C over the entire range is also important for BT thermometers [15].

The relation for temperature T-dependent voltage V across a PN junction at constant forward-bias current I can be expressed by:

$$I = Ae^{\frac{qV - E_g}{kT}}.$$

If the PN junction is driven by two different forward-bias currents I_1 and I_2, corresponding voltage drops V_1 and V_2 will be produced as below:

$$V_1 - V_2 = \frac{kT}{q}\ln\frac{I_1}{I_2},$$

where A is a constant depending on the geometry of the junction, q is the electron charge, E_g is the band gap energy and k is the Boltzmann constant.

When the ratio of two driving currents is maintained constant, the voltage difference is linearly proportional to the temperature. Thermometers based on this principle can be realized either by applying a square-wave current to a PN junction [16] or by using two matched devices operating at different current levels [17].

A thermocouple uses the Seebeck effect as a thermoelectric transducer. The Seebeck effect is the phenomenon when two dissimilar conductors or semiconductors are connected at two ends; once a temperature difference between the two junctions exists, a voltage gradient will be generated that depends on the temperature difference between the two junctions.

The sensitivities of some typical thermocouples in the temperature range of 20–40 °C are about 41 μV/K for copper/constantan, about 40 μV/K for chromel/alumel, and about 6.1 μV/K for platinum/platinum–rhodium (10%) [15].

Multiple thermocouples can be connected in series or in parallel to form a thermopile transducer to improve the sensitivity up to 36.5 mV/K [18].

Besides the thermal conduction mechanism, which is utilized to sense temperature by the above transducers, thermal radiation power emitted from an object with a temperature

above absolute zero is used to measure the temperature of the object.

The thermal radiation power emitted from a human body can also be used to measure BT. The peak of the thermal radiation from a human body lies in the far-infrared region. Infrared transducers for BT measurement require sensitivity to the range 7–14 μm, which covers the energy spectrum of thermal radiation from the body surface.

There are three types of infrared transducers: thermal transducers, photon transducers (also called quantum detectors) and radiation field transducers. The radiation field transducers respond directly to the radiation field but have not been widely used since the 1970s.

In thermal transducers, the incident infrared radiation is absorbed to change the substrate temperature, and the resultant change in some physical property is used to generate a proportional electrical output. They are wavelength independent and can be operated at room temperature and used in uncooled thermography systems, but the response is slow and noisy.

Photon transducers detect incident photons caused by fundamental optical excitation processes in semiconductors. The output electrical signal is proportional to the changed electronic energy distribution. Although they need cooling equipment and the sensitivity is wavelength dependent, they are highly sensitive and fast in response, and are commonly used in infrared spectroscopy and infrared thermography [19].

2.1.2 Instrumentation

Temperature transducers are used to convert heat energy or temperature into other forms of energy, and finally into an electrical signal. The electrical signal is processed by the succeeding instrumentation for noise suppression, calibration, conversion and visualization of BT values. Instrumentation can be divided into different measurement modes by its method of processing the measured signal to temperature readings.

2.1.2.1 Actual and predictive measurement Most commercial automatic electronic thermometers for both SBT and BBT use two measurement modes, actual and predictive, to acquire BT readings, as shown in Fig. 2.

The actual measurement measures the actual temperature of a specific region at a specific moment by mercury thermometers or by automatic electronic thermometers. The thermometer is placed on a body surface until the temperature does not change any more or reaches the thermal equilibrium stable temperature. It may take more than 10 min in the armpit, and about 5 min in the mouth.

Predictive measurement uses a previously calibrated curve of temperature–time course and the actual measurement of the first 30 to 90 s to predict the final equilibrium temperature value. It dramatically reduces the measurement time needed in actual measurements [20]. The latest thermometers are able to give BT readings in only 4 s without being affected by extraneous factors [21].

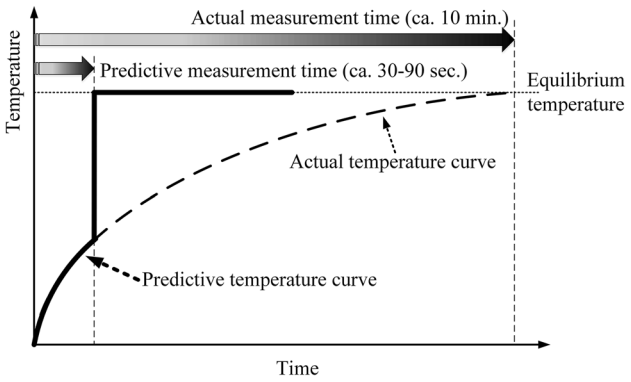

Fig. 2 Temperature–time courses of actual measurement and predictive measurement of BT [20]

2.1.2.2 Invasive and noninvasive measurement Because SBT measured at some commonly used positions such as axillar, sublingual or tympanic does not always reach satisfactory reliability to reflect the body operating temperature accurately, measurement of CBT is indispensable, especially in the operating room and prolonged hard-working occupations where real-time monitoring of CBT is preferable and more reliable than SBT.

The original measurement of CBT required surgical insertion of a transducer head inside the human body invasively. The transducer head is made commonly as a needle-type, or a catheter-type as shown in Fig. 3.

Several positions, such as rectum, esophagus, pulmonary artery and urinary bladder, are used to measure CBT invasively in medical settings. The rectum is one of the most common positions, especially in babies and children although it is not suitable for rapid change measurement due to its delayed response. Esophageal CBT is measured by inserting a flexible transducer head through the mouth or nose during anesthesia. The esophagus is preferred because of its rapid response and its position close to the aorta and to the blood flow toward the hypothalamus. The aorta artery is considered the most accurate position because the artery blood from the deep body is measured directly using a catheter-type transducer.

To measure CBT in the digestive tract, an ingestible capsule-type thermometer in which a temperature transducer and a radio transmitter are encapsulated is used. The CBT profile can be tracked continuously during the process when it is swallowed and moves toward the rectum and finally is expelled from the rectum. One of the commercial products

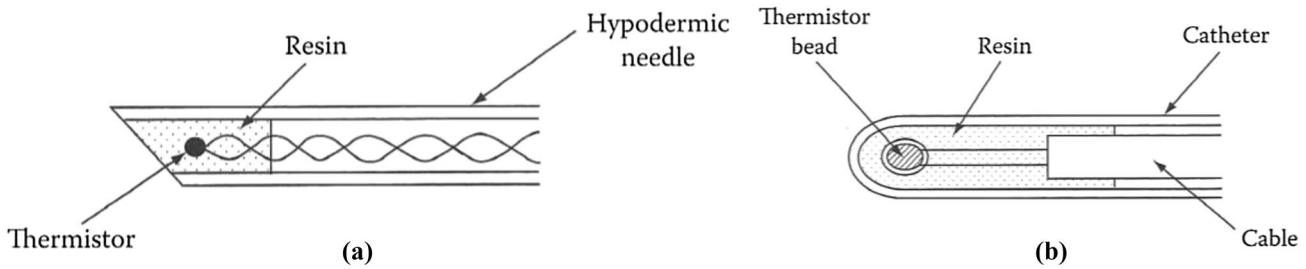

Fig. 3 Transducer heads in which the thermistor is connected to a flexible insulated cable, and the connected part is also insulated and completely waterproof. **a** Needle-type; **b** Catheter-type

(CorTemp®, HQ Inc., Palmetto, FL, USA) and the measured continuous CBT profile are shown in Fig. 4 (left and right, respectively). It is 2.75 g in weight, 23 mm in length and 10.25 mm in diameter. As the capsule moves along the digestive tract, it transmits the CBT values every 20 s wirelessly to an external receiver.

Invasive CBT measurement causes subject discomfort and irritation due to inserting a probe and is undesirable even in medical settings. The ingestible capsule thermometer provides an acceptable level of accuracy as a surrogate measure of CBT without causing too much discomfort to the subject. This form of CBT measurement allows CBT to be measured continuously and has gained wider acceptance in the last decade [23].

An ideal position for measuring CBT should meet the following three requirements: (1) harmless and painless, (2) uninfluenced by local blood flow or other environmental factors, (3) track small changes of arterial blood temperature rapidly and reliably [24].

Invasive methods using the body's natural orifices do not satisfy the first requirement during prolonged patient monitoring and especially in babies and small children. Although invasive measurement of CBT can give accurate readings, such methods have very complex manipulation procedures, their usage is strictly limited only to medical settings.

Several noninvasive methods required only from body surface have been developed to measure CBT since the early 1970s.

The zero-heat-flow method was proposed to estimate CBT noninvasively from the temperature measured on the skin surface by a probe consisting of two thermistors, a piece of nylon gauze and a thin-film heater element. These components are encapsulated in a multilayer sandwich using silicone rubber as shown in Fig. 5 [25].

The two thermistors form two arms of a Wheatstone bridge, and the out-of-balance signal from the bridge controls a heater circuit through a comparator amplifier and a Schmitt trigger. The principle is based on heat insulation between two thermistors and their equalization when no heat flow exists. Two matched thermistors are sandwiched at the center by two insulating layers. The lower layer is tightly attached to the skin surface. A heater covers the upper insulating layer. The temperature difference between the two thermistors is detected and the heater is controlled to keep

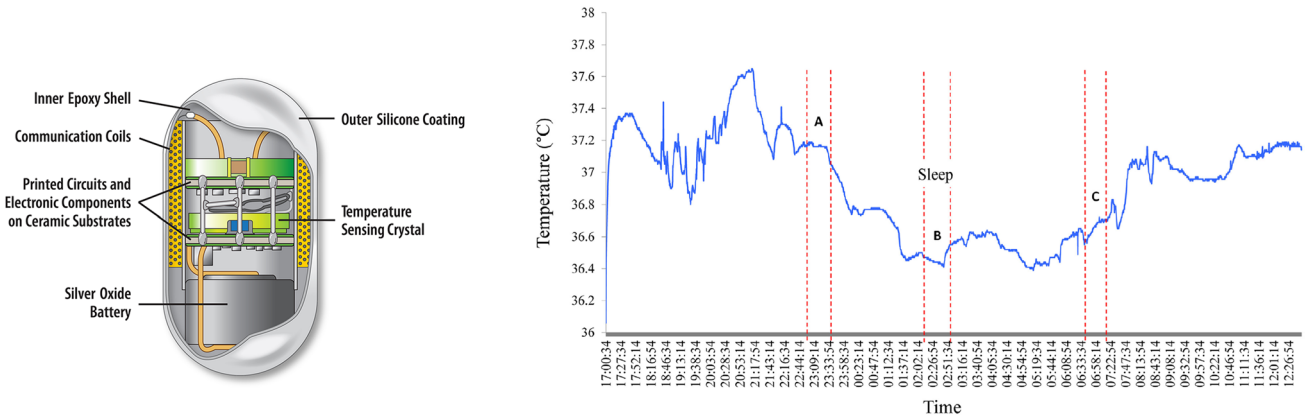

Fig. 4 Ingestible capsule thermometer (CorTemp®) and the measured CBT profile in a subject. Three regions by dotted red lines indicate **a** the highest 30-min average value before sleep onset, **b** the lowest 30-min average value during sleep and **c** the first 30-min average value after arousal [22]

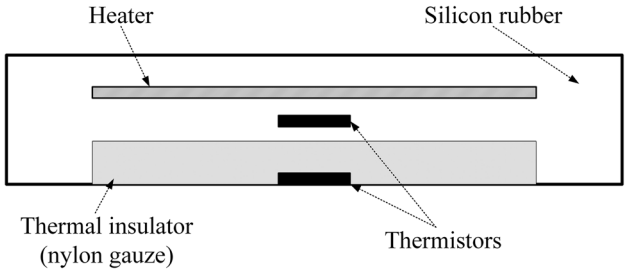

Fig. 5 Diagrammatic structure of zero-heat-flow transducer head

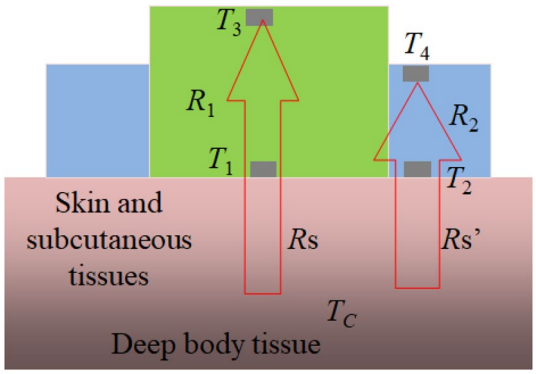

Fig. 6 Diagrammatic structure of the dual-heat-flux transducer head. Two channels of heat flux are formed when the body surface is covered by two kinds of heat insulators with different thermal resistances, R_1 and R_2. R_S and R_S' are the thermal resistances of the skin and subcutaneous tissues along two channels; T_C is the CBT; T_1 and T_2 are the measured skin surface temperatures beneath the insulator; T_3 and T_4 are the temperatures at the upper surface of the insulator

both thermistors at the same temperature, or to minimize heat flow between both thermistors. Finally, the skin temperature may equilibrate with a deep temperature [26].

This method was theoretically analyzed and experimentally validated by successive studies [27, 28]. The structure of the original transducer head was improved to secure better heat insulation and to maintain the circumference temperature as same as the center.

Because the zero-heat-flow method requires considerable power for the heater element to balance the difference between the two thermistors, bulky size and heater usage are not suitable for miniaturization and long-term measurement. The dual-heat-flux method without the heating element was proposed as shown in Fig. 6 [29].

The transducer head was built structurally to form two different thermal pathways comprising dual heat-flux channels. Each channel has a pair of temperature transducers attached to its two ends to measure the temperature. When four temperatures, $T_{1–4}$, at four points are measured and two thermal resistances R_S and R_S' in subcutaneous tissues at two channels are supposed identical, simultaneous equations can be established to solve the CBT value T_C without knowing the thermal resistance in the subcutaneous tissues.

$$T_c = T_1 + \frac{(T_1 - T_2)(T_1 - T_3)}{K(T_2 - T_4) - (T_1 - T_3)}$$

The thermal resistance ratio K of the two thermal insulators is determined through experimental calibration.

$$K = \frac{(T_0 - T_2)(T_1 - T_3)}{(T_0 - T_1)(T_2 - T_4)},$$

where, T_0 is the preset water temperature in a calibration thermostat.

Nevertheless, both methods above are not able to specify what depth of CBT beneath the skin is measured. Other aspects such as the effects of probe structure and thermal insulators on measurement performance and response time remained ambiguous.

Through mathematical simulation by building a three-dimensional finite element method model based on information from abdominal anatomy and transducer head geometry, the dual-heat-flux method was theoretically evaluated. By integrating biophysical and physiological knowledge into the model, it is possible to estimate the CBT distribution from cutaneous SBT measurements using an inverse quasi-linear method and 16-thermistor arrangement surrounding the abdomen [30].

By optimizing the geometrical structure (height and diameter) and heat insulator materials (rubber sponge, copper and aluminum) of the transducer head, the depth of CBT measurement was theoretically studied. The transducer head with the larger area is confirmed to measure the deeper position of CBT in the simulation results. The depth of measured CBT is estimated to be 7.6 mm beneath the body surface [31].

2.2 Mathematical approaches

It is well known that HR and BT show positive correlations to maintain the thermal homeostasis of the body during physical activity. Not only physical and mental activities affect BT stability but also many endogenous and exogenous factors can impact on BT. To understand a general principle for the phylogenetic development of thermoregulatory mechanisms, the interactive dependency of CBT on other vital signs, such as HR and BR, BP, cardiac output and circulation time, environmental factors and anthropological characteristics have been investigated intensively since the 1940s [32].

Because of interdependencies and interweaving among CBT, SBT, other vital signs, mental and physical activity levels, environmental variables such as clothing condition, surrounding climate temperature and humidity, several

mathematical modeling methods have been developed by using thermoregulatory mechanisms-based principles to estimate CBT indirectly from variables rather than only temperature measurement.

2.2.1 Multiple regression model

Linear and multiple variable regression analyses were used to investigate the dependency of BT on other vital signs. The change rates of HR (ΔHR/°C) and BR (ΔBR/°C) on variations in BT were estimated by collecting data from a large population consisting of 2,219 males and 2,274 females. The ΔHR/°C and ΔBR/°C were approximately 7.2 ± 0.4 bpm and 1.4 ± 0.1 brpm, respectively. When integrating other factors such as age, oxygen saturation and mean blood pressure, the results became 6.4 ± 0.4 bpm and 1.2 ± 0.1 brpm, respectively. However, the related studies on the relationship between BT, HR and BR did not always produce consistent outcomes. ΔHR/°C can reach as high as 14.7 bpm, and has a mean value of 9.7 bpm. ΔBR/°C is mostly within a range of 2.0–4.0 brpm [33].

To estimate CBT, 30 parameters, including physiological, physical and environmental ones such as HR and BR, SBT at 11 positions, and relative humidity were measured under different clothing, activity and climatic conditions. A stepwise multiple regression analysis was used to determine which of 30 parameters (SBTs, HR, BR, temperature and humidity inside the clothing front and back, body mass, age index, body fat, sex, clothing, VO_2, thermal comfort, sensation and perception and sweat rate) was the largest contribution to the model. Through an investigation by a bootstrap methodology, the best model in terms of feasibility and validity predicts CBT with a standard error of estimation of 0.27 °C and adjusted R^2 of 0.86 with a comparison to rectal temperature [34].

2.2.2 Autoregressive (AR) model

Various factors that affect the thermoregulatory system can be used as exogenous inputs to the model. These factors may include several aspects: (1) environmental: mean radiant temperature, ambient temperature, relative humidity, wind speed, (2) activity: walking speed, pack weight (load), terrain factor, slope/grade, water intake, (3) individual characteristics: age, weight, height, fat percentage, (4) clothing: insulation and permeability.

By considering the large thermal inertia in the body, a data-driven approach based on an autoregressive (AR) model can be built to predict CBT using exogenous data and past CBTs as inputs.

In the training phase, the AR model coefficients are tuned by minimizing the difference between estimated CBT and reference CBT. The model order is determined by some analytical criterion such as the minimum description length and Akaike information criterion, or by cross-validation. If a training dataset can be collected with enough variety, a proper regularized model would be made individual-independent, thus significantly simplifying the procedure for individual training in constructing individual-specific models [35].

By collecting the reference CBT using a telemetry capsule, an individual-specific AR model was trained to predict the CBT variations 20 min ahead using the previous CBTs and the current HR [36]. A real-time implementation of an AR-based algorithm for predicting CBT was developed, and the performance of the algorithm was assessed in terms of its prediction accuracy and the root mean square error (RMSE) [37].

2.2.3 Thermoregulatory model

A mathematical model based on thermoregulatory mechanisms consisting of a series of heat-transfer equations was built to predict real-time CBT by using the primary metabolic activity as inputs that are derived from HR and ambient temperature, and other individual anthropological characteristics (height, weight and clothing).

The model uses individual values, group means or default population values of anthropological characteristics, real-time measured HR and local environmental parameters (ambient air temperature, wind speed, relative humidity, and radiant load) as the input variables to estimate CBT.

The model was validated using data collected from varied environments, clothing and heat acclimation status. Overall, CBT predictions corresponded well with measured values (root mean square deviation: 0.05–0.31 °C) [38].

2.2.4 Kalman filter

A Kalman filtering method was proposed to estimate the continuous time course of CBT in an ambulatory environment using a series of HR measurements [39]. The model was trained using data from 17 volunteers engaged in a 24-hour military field exercise (air temperatures 24–36 °C, relative humidity 42–97% and CBT 36.0–40.0 °C), and was validated by data from 83 subjects in the laboratory and field, including various combinations of temperature, hydration, clothing and acclimation state. The performance was evaluated by the Bland–Altman method using CBTs measured by ingestible capsules as a reference. The results showed that the overall bias is -0.03 ± 0.32 °C, and 95% of all CBTs among more than 52,000 estimates fall within ± 0.63 °C.

An original Kalman filter consists of "time update procedure" and "measurement update procedure." An extended Kalman filter was proposed to improve CBT estimation

accuracy by exploring various orders of "observation models" in "measurement update procedure" to find the best model [40].

After examining 11 HRV parameters, namely, nMHR, SDNN, RMSSD, pNN50 in the time domain, and LF, HF, TF, VLF, nLF, nHF, LF/HF in the frequency domain, nMHR, nLF, nHF and LF/HF were found the best inputs to estimate CBT with RMSE no more than 0.40°C in 10 subjects (6 subjects were used for training and 4 subjects were used for test).

From the point of view of physiological significance, nMHR is removed from its HR baseline, which is different from individual to individual, and demonstrates better performance than MHR. nLF and nHF quadratic fitting curves can satisfactorily follow CBT rhythmic changes. LF/HF reflects sympathetic–parasympathetic balance, which regulates BT.

3 Thermometry modalities

With comparison of temperature measurement in industrial fields, besides the three requirements mentioned above in the measurement of CBT, some special requirements imposed on measurement of BT are (1) sterilization should be available to fulfill basic hygiene standards when a thermometer is used across individuals repeatedly; (2) maximum safety and minimum disturbance to the organs, tissues and physiological conditions should be guaranteed in various environments, such as electromagnetism, heat, radiation, vibration; (3) minimum constraint and minimum uncomfortable for the human body should be committed; (4) good repeatability and high reliability, high biological affinity and low toxicity should be realized; (5) compatibility with inherent variability among individuals from infants to adults and elders is required; (6) application-dependent selectable accuracy and response time is desirable; (7) scenario-dependent disposable or reusable usage should be provided.

Various modalities of thermometers to acquire BT and match different application scenarios have been developed over the past several decades [41].

3.1 Invasive and noninvasive

From the point of view of intervention, thermometers can be divided into three main modalities: noninvasive, semi-invasive and invasive. Noninvasive methods usually measure BT on the body's superficial positions, such as axilla, groin, external auditory canal, forehead, neck and thorax. Semi-invasive methods require a temperature transducer to be placed inside the body through a natural body orifice such as mouth or tympanum without too much undue discomfort. Invasive methods require the temperature transducer to be inserted into a deep body position such as rectum, vagina, esophagus, nasal cavity, bladder, digestive tract and blood vessel.

3.2 Contact and noncontact

From the point of view of thermal transfer mechanisms, there are three main modalities, conduction, convection and radiation, used in the measurement of BT. Contact measurement uses the thermal conduction mechanism by contacting the temperature transducer to the measurement target position like many SBT measurements. Spontaneous heat transfer occurs from the target region of high temperature to the transducer of lower temperature by the direct microscopic exchange of kinetic energy to reach the same temperature at the point in thermal equilibrium. Noncontact measurement uses heat convection and radiation through blood flow and breath gas, and by means of photons in electromagnetic waves.

3.3 Direct and indirect

From the point of view of the signal source, there are two main modalities: direct and indirect measurements. Direct measurement of BT senses temperature directly by various temperature-sensitive transducers through converting the heat energy to other forms of energy such as volume, density, resistivity, velocity and electricity. Indirect methods utilize the thermoregulatory mechanisms and the interactive relationship among BT, endogenous vital signs and latent exogenous environmental factors to estimate BT indirectly.

3.4 Free and restrained

From the point of view of usability, there are two main modalities: daily healthcare oriented and medical checkup oriented. Daily healthcare oriented thermometers are made for long-term and short-term usage in a free style noninvasively and are usually integrated into some daily life necessities in several ways, such as touchable, wearable and invisible. BT values measured by these thermometers commonly have relatively poor BT accuracy and reliability due to untrained personal manipulation. However, a large volume of BT data collected over a long-term period can help overcome these shortcomings. Medical checkup-oriented thermometers are made for use in medical and clinical settings by professional personnel. They are usually expensive and complex, commonly used in restrained manners in a clinic visit for a short-term noninvasively, and ICU and surgical operating room invasively.

3.5 1-D and n-D

From the point of view of data presentation in temporal and spatial domains, thermometers usually provide one-dimensional measurements on a local spot sporadically or continuously, while thermographs provide two-dimensional measurements on a local area as a thermal distribution image statically or dynamically. By combining thermal images with other anatomical and functional information from MRI/CT images, three-dimensional (3-D) or higher-dimensional thermal images can be obtained for accurate diagnosis and reliable therapy simultaneously, especially for medical applications where temperature changes are clinically significant [42]. There are several techniques, such as infrared thermography, microwave, ultrasound and electrical impedance for noninvasive thermographic imaging.

4 Interpretation of BT

BT is a holistic resultant regulated by thermoregulatory mechanisms through interaction with many endogenous and exogenous factors. Comprehensive interpretation of the physiological significance of BT is one of the most important tasks in clinical applications. The normal mean BT value has been widely investigated since the mid-19th century. Davy reported a mean value of 36.9 °C for the oral temperature obtained during the working day in 1845, while Pembrey and Nicol found it to be 36.2 °C. Schaefer summarized the oral temperatures obtained by eight groups over 50 years from 1848 and found it to be 36.8 °C [43].

Wunderlich reported 37.0 °C as the mean BT and 36.2–37.5 °C as the normal range of BT for healthy adults after a statistical investigation based on several million measurements in the armpit obtained from about 25,000 subjects since 1861. BT readings above 38.0 °C are always "suspicious" and "probably febrile." He also identified the time-variable property of BT that reaches its minimum between 2 and 8 AM and its maximum between 4 and 9 PM [2].

However, the mean value of 37.0 °C for the oral temperature is constantly questioned. Inconsistency in the mean value of BT continues to be debated.

An intensive study based on 148 healthy adults was conducted using an automatic digital thermometer on oral measurement one to four times daily for three consecutive days. The findings confirmed that 36.8 °C was the mean oral temperature; 37.7 °C was the upper limit of the normal temperature range. BT varied with time of day having a minimum at 6 AM and maximum at 4 to 6 PM, and a mean amplitude of variability of 0.5 °C; women had slightly higher normal temperatures than men [44].

A systematic review was performed by investigating the literature published from 1935 to 1999, and found that the normal BT range was 33.2–38.2 °C for oral, 34.4–37.8 °C for rectal, 35.4–37.8 °C for tympanic and 35.5–37.0 °C for axillary. The ranges in oral temperature for men and women were 35.7–37.7 °C and 33.2–38.1 °C, respectively; 36.7–37.5 °C and 36.8–37.1 °C in rectal, and 35.5–37.5 °C and 35.7–37.5 °C in tympanic. When assessing BT, it is important to take measurements of position and time, subject's age and gender into consideration [7].

Although the determination of the so-called normal BT value still remains in debate, there is no doubt that BT contains valuable health- and pathology-related information. Most of the conventional styles of thermometers measure BT once at a time on a specific spot, and are commonly used for real-time applications such as fever diagnosis, thermotherapy and heatstroke prevention. The new style of thermometers can provide continuous monitoring of BT automatically at a certain interval over some periods for long-term applications such as circadian rhythm and cognitive performance.

Because BT depends on many factors, such as measurement position, time of day, sex, pathological condition, physical and mental stress level, comprehensive interpretation of BT's physiological significance should take these factors into consideration. There are two analysis approaches for interpretation of BT significance in clinical applications. In real-time applications, an instant absolute value in terms of rapid response and accuracy is critical. In long-term applications, relative change, reliability and repeatability are usually paid more attention.

4.1 Real-time applications

Normal BT (normothermia) is maintained within a limited range of 36.5–37.5 °C by thermoregulatory mechanisms [45]. Out-of-range BT is considered significant in relation to various pathological conditions and clinical syndromes. Real-time measurement of BT has found many applications in health condition screening and clinical monitoring, such as fever checkup, heatstroke diagnosis, surgery and nursing management, and thermal therapies. Real-time applications commonly utilize an absolute and an isolated value of BT measurement in making decisions, which is basically based on systematic statistics and threshold ranges, and usually require accurate measurement and quick response to local temperature change.

When the BT set point is disturbed by infectious or noninfectious diseases, as a normal adaptive response and self-protective mechanism, fever (pyrexia, febrile response) would occur to trigger increased muscle contractions, result in greater heat production and efforts to conserve heat. The raised set point was reflected in significantly elevated BT. Fever is generally diagnosed as CBT (rectum) at 37.5–38.3 °C or SBT (armpit) above 37.2 °C, or an early morning oral BT above 37.2 °C or a late afternoon oral BT

above 37.7 °C. Lower thresholds are sometimes applicable to frail elders [46].

High BT is an indicator of febrile disease and may be caused by insufficient heat dissipation due to dysfunction of the autonomic circulatory system, insufficient sweat gland secretion and compromised peripheral blood perfusion. During prolonged sports activities or strenuous physical work in a hot environment of 25 °C or above, sometimes even in a cool environment, frail and aged persons are prone to be afflicted by heatstroke. Moreover, if subjects wear heavy and sealed clothing, their CBT would rise to above 38.5 °C in minutes. Heatstroke precaution and BT monitoring are necessary in the summer season for outdoors activities [47]. To quantify heat strain, real-time monitoring of HR and CBT (rectum) or SBT is required. A wearable helmet with a built-in noninvasive skin temperature sensor is used [48].

A surgical operation is either a life-saving or a life-threatening process that greatly affects BT. Both general and local anesthesia suppress afferent and efferent control of the thermoregulatory system, and lead to a decrease in heat production and thermoregulatory capability. Additional heat loss is caused via radiation, conduction, convection and evaporation. Preheating and hypothermia management to maintain SBT and CBT between 36.0 and 38.0 °C during intraoperative and postoperative periods are of critical importance [49].

Real-time thermal imaging for assessing SBT is indispensable in thermal therapy, which is based on a wide range of heat effects on biological reactions.

Hyperthermia uses high-intensity thermal energy to provide thermotherapeutic effects by heating the target region of tissue to cause the defined regions of protein denaturation, cell damage and coagulative necrosis at specific controlled temperature elevation and the duration of exposure time. By using electromagnetic energy, focused ultrasonic energy and other thermal-conduction-based methods as heating sources, thermal therapy has found many promising applications in oncology, physiotherapy, urology, cardiology, ophthalmology and so forth. Thermal therapy techniques include hyperthermia (40–41 °C), moderate-temperature hyperthermia (42–45 °C) and thermal ablation or high-temperature hyperthermia (> 50 °C) [50, 51].

Hypothermia (cryotherapy) decreases body (skin and tissue) temperature by using various methods, such as whole-body cryotherapy, coolant sprays, cryotherapy cuffs, frozen peas, ice baths or packs, and even a probe administered into the target tissue. Hypothermic effects facilitate the release of hormones such as adrenaline, noradrenaline and endorphins, freeze malignant cells, resist the inflammatory and oxidative stress responses, decrease nerve conduction velocity and decrease tissue metabolism. It is widely used to reduce migraine symptoms, numb nerve irritation to treat pinched nerves or neuromas, chronic pain or even acute injuries, analgesia, treat mood disorders such as anxiety and depression, reduce arthritic pain, multiple sclerosis and rheumatoid arthritis, treat low-risk tumors for certain types of cancer, including prostate cancer, prevent dementia and Alzheimer's disease, treat atopic dermatitis and other skin conditions, reduce edema, laminitis prophylaxis and treatment [52, 53].

4.2 Long-term applications

In comparison to real-time applications, accumulation and comprehensive analysis of BT measurement over a long-term period help find more valuable information for the diagnosis of diseases, chronomedicine and daily healthcare.

BT variability (BTV) comes from both endogenous and exogenous sources. Endogenous sources include somatic sites, biorhythms (circadian, menstrual and annual), fitness, gender and age. Exogenous sources include disease incidents, external factors in the environment, diet and lifestyle.

Instead of simple thresholding methods, various complicated algorithms can be applied to a large volume of BT measurements over a long-term period comprehensively to extract characteristic features and significant information.

Although the set point is maintained within a narrow range around 37.0 °C by the thermoregulatory mechanisms in spite of fluctuations in environmental variables, it does not stay strictly constant. The daily variation of the set point demonstrates the circadian rhythm and reflects on the BTV. The cosinor analysis method is commonly used to analyze long-term BTV biorhythms such as the circadian rhythm, menstrual cycle, alertness and performance rhythms [30].

CBT data were measured from bedridden patients with sequelae of cerebral infarction by a zero-heat-flow thermometer at an interval of 3 min for 2.5 days. The single cosinor and the multivariate cosinor methods were used to determine the rhythm of the whole group of patients. The result revealed multiple distinctive biorhythms in addition to circadian biorhythm in bedridden patients with sequelae of cerebral infarction [54].

A wavelet transform is also used to characterize the ultradian and circadian rhythms of CBT. Two-whole-days' CBT from two female bedridden elders suffering from cerebral infarction sequelae, were analyzed by the stationary wavelets transform (SWT). The results showed that SWT can faithfully reveal the time–frequency information of feature elements (peaks and troughs) of the rhythmicity [55].

Because female ovulation causes a sustained increase of BBT of at least 0.2 °C, the menstrual cycle demonstrates a biphasic pattern, or lower value before ovulation, and higher value afterward in a BBT profile. Oral BBT were traditionally used to evaluate fertility and thyroid function in a clinic. By simultaneously collecting SBT and CBT during sleep automatically using two continuous thermometers every 10 min with accompanying morning oral BBT for 6 months,

a hidden Markov model is applied to estimate menstrual cycles indicating ovulation days and menstrual periods from three kinds of BT measurements, SBT, CBT and BBT. The comparative performance evaluation results shown that all three kinds of BTs can estimate the biphasic property in a menstrual cycle, CBT has the best accuracy, BBT is slightly lower accuracy but competitive enough with CBT, SBT has the poorest performance due to severe measurement artifact. It is also confirmed that reliable relative changes instead of accurate absolute values of BT are more important in estimating the biphasic property in a menstrual cycle [56–58].

The sleepiness–wakefulness cycle is a typical circadian rhythm and demonstrates a propensity synchronization with CBT. Sleep is most conducive in the minimum phase of BT during the day but is inhibited in a "wake maintenance zone" before the minimum phase. Insomnia, hypersomnia and circadian rhythm-related sleep disorders such as delayed sleep phase syndrome (DSPS) and advanced sleep phase syndrome (ASPS), have been linked to abnormal BT rhythms, such as delayed or advanced in timing abnormality, and elevated CBT nocturnally or diurnally. DSPS and ASPS insomnia may be related to impaired thermoregulatory function, particularly a reduced ability to dissipate body heat from distal skin areas [59].

Besides the above applications, analysis of biorhythms from BTV found relevant causality with a variety of disease conditions, such as allergy, brain lesions, cancer, chronic fatigue syndrome, depression, febrile states, HIV infection, obesity, psoriasis and thyroid function [6].

In chronomedicine, BT is used as an indicator for determination of the optimal delivery timing of minimum drug dosage for cancer treatment. In the administration of radiative therapy for patients suffering from tumors, the tumor temperature was used as a temporal marker to schedule treatments. More than 60% of patients who received treatment when the tumor was at peak BT were alive and disease-free 2 years later. This is perhaps because the highest metabolic activity at peak BT enhanced the therapeutic effect [60].

5 Prospect

About 150 years ago, Wunderlich had predicted that "thermometry will doubtless lead to entirely new view of many diseases, and no small part of our pathology will have to be radically reconstructed" [2]. The clinical significance of BT in medical and healthcare applications should be realized by two aspects: thermometry and analytics.

Besides current existing styles of thermometers for medical use and daily healthcare, various thermometry modalities for application in various scenarios will be developed to satisfy fundamental requirements toward more affinity to biological systems, improved usability and better accuracy. A thorough investigation of the aspects of BT thermometry was reviewed [41]. Specifically, in daily healthcare applications, the constantly evolving thermometers can be roughly classified into three categories as touchable, wearable and invisible.

Touchable thermometers measure BT by simply touching the body surface intentionally, constantly or occasionally. They are commonly in forms such as a skin patch, flexible adhesive tattoo, bandage, an accessory of a smartphone, and even a built-in function in a smartphone.

Wearable thermometers can be worn by a user during daily activities. They are usually integrated into items, such as a watch, earphone, eyeglass, ring, vest, gloves, belt, shirt, brassiere and helmet, as an inseparable component. An individual customized size is commonly required. They can measure BT ubiquitously with the user moving without any apparent or obtrusive parts.

Invisible thermometers are embedded into living ambient items (beds, chairs, dressing mirrors [61], and ceiling lamps) completely without the user's awareness. They are usually immobile and measure limited regions in fixed positions. They can measure SBT contactlessly and unintentionally but automatic individual identity recognition is indispensable.

With the rapid advancement of IoT infrastructure and big data analytics platforms, by combining mature BT measurement technologies, various BT can be continuously and ubiquitously measured with very little or even no cost by proper thermometry modality in a variety of life scenarios whether at home, in the office or while moving, a huge volume of BT data can be automatically accumulated over a long-term period.

Moreover, at the time of BT measurement, if other vital signs such as BP, HR, BR, activity strength, skin humidity, evaporation rate, heat flow and sweat volume, as well as other individual anthropological parameters and environmental factors can also be measured simultaneously, the comprehensive interpretation of its physiological significance will be accelerated by AI algorithms and other data-driven modeling methods. More value-added applications and applicable areas will be explored more efficiently in depth.

Just as it is difficult for us to imagine the plot of a film by just seeing the last scene of the film, sometimes it is not easy to make sense of the physiological significance from an instant BT value. On the other side, out-of-range BT is considered significant combined with various pathological conditions and clinical syndromes; nevertheless, most of the time, a single BT value is not always reliable enough, and usually accompanies poor accuracy, interruption and inconsistency, and low information density. These adverse aspects can be alleviated by applying proper big data analytics algorithms. In contrast to a real-time application, which usually requires accuracy, quick response and rapid decision-making, long-term application prefers repeatability and reliability. Instead of an absolute value, the relative change is more important in long-term monitoring. Some in-depth

data mining algorithms can relieve the severe requirements on the accuracy of measurement.

Real-time applications for diagnosis and therapy in medicinal settings are based on massive statistical thresholding approaches, while long-term applications of at-home use for daily healthcare are based on personalized adaptive modeling methods.

Big data analytics opens a new era for long-term application in the healthcare and medical domains. "Google flu trends" estimated the flu activities worldwide by modeling tens of millions of search queries to detect influenza epidemics in areas with a large population of web search users instead of epidemiological investigation [62].

A study analyzed the relationship between BT and BP, the results showed that the relationship does not only depend on the central nervous system but also is a part of the basic integrative mechanisms [32, 63].

In addition to BT and BP, biorhythmic variations in other vital signs, such as HR, saliva, urine, blood and cell proliferation, have been quantified to identify normal and risky patterns for diseases, to optimize the timing of treatments such as nutraceuticals using antioxidants for preventive or curative healthcare [64]. Modern chrono-related studies are now expanding in both dimensional and functional scales, from the genome level to the whole-body level, and from fundamental chronobiology to medical applications, such as chronophysiology, chronopathology, chronopharmacology, chronotherapy, chronotoxicology and chronomedicine. All of these topics are rooted in the study of biorhythmic events and their adaptation to endogenous and exogenous stimulants, and are still exciting challenges for new discoveries.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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