Thermomicrofluidics for biosensing applications

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Abstract
The accurate detection of biological systems containing biomolecules and bioparticles is increasingly important in diverse research fields, particularly in analytical and biological chemistry. Implementing thermophoresis in microfluidic devices (thermomicrofluidics) enables the manipulation and measurement of biomolecules and bioparticles in a label-free and high-precision manner, providing a promising avenue for biosensing. This review presents fundamentals of thermophoresis and its coupling with other thermal-induced physical phenomena in the microfluidic setups. We overview the capabilities of thermomicrofluidics for diverse biosensing applications such as monitoring of biomolecular interactions, detection of nucleic acids, profiling of extracellular vesicles, and manipulation of cells. Biosensing by thermomicrofluidics provides insights into physiopathological processes and disease diagnostics. Current challenges and further directions of thermomicrofluidic detection are discussed.

KEYWORDS
biomolecules, bioparticles, detection, microfluidics, thermophoresis

1 INTRODUCTION

Microfluidic technologies have gained popularity for biosensing by offering advantages of precision manipulation of particles and fluids, small sample consumption, and ability to integrate a variety of biochemical reactions.1–8 Most microfluidic methods for biosensing applications rely on the immobilization of targets at the liquid-substrate interface for biological recognition and signal transduction or amplification.9–12 However, interface-based sensing suffers from the nonspecific adsorption and low-mass transport efficiency for detecting complex biological systems.13,14 Moreover, as the biological system
is comprised of a wide range of proteins, nucleic acids, extracellular vesicles (EVs), and cells,\textsuperscript{15–19} the versatility of microfluidic sensing strategies for various biological targets has to be taken into consideration.

Implementing thermophoresis, the directed movement of a suspending particle along a temperature gradient, in microfluidic devices (thermomicrofluidics) provides a versatile, homogenous means for biosensing applications.\textsuperscript{20,21} For example, thermophoresis is highly sensitive to physicochemical parameters (such as size, charge, permittivity, hydration shell, and conformation change) of biomolecules,\textsuperscript{21–24} which can be used as a measure of biomolecular interactions in microfluidic devices.\textsuperscript{25,26} The coupling of thermophoresis with other thermal-induced physical phenomena,\textsuperscript{27–29} such as convection, diffusiophoresis, and thermoelectric effect inside microfluidic devices further enables precise manipulation and in situ signal amplification of bioparticles for disease diagnostics.\textsuperscript{30–32}

In this review, we introduce the basic principles of microfluidic thermophoresis and its coupling with other thermal-induced physical phenomena for biosensing applications. We provide a brief overview of practical utility of thermomicrofluidics in characterizing biomolecular interactions and detecting various biomarkers of biological systems. We then conclude with a discussion of limitations and directions of thermomicrofluidic biosensing.

\section{Fundamentals of Thermodiffusiophoresis}

\subsection{Mechanisms of thermophoresis}

Owing to the advantage of small characteristic scale, the microfluidic device can induce a strong temperature gradient ($\nabla T$) with a slight temperature rise ($\Delta T$), allowing thermophoretic manipulation and measurement of biomolecules and bioparticles without disrupting their integrity. Diverse approaches have been used to create $\nabla T$ in microfluidic devices, including heating water body\textsuperscript{33} or metallic substrate\textsuperscript{34,35} by laser, transferring heat from the heat source/sink\textsuperscript{36} and electrodes-induced Joule heating,\textsuperscript{37} depending on the specific application scenarios. The velocity of thermophoresis is described as $-STD\nabla T$, where $ST$ is the Soret coefficient and $D$ is the Brownian diffusion coefficient. Generally, most biomolecules and bioparticles exhibit positive $ST$ in an aqueous solution around room temperature, implying that their thermophoresis directs from hot to cold (Figure 1A).\textsuperscript{23} The counterbalance between thermophoretic depletion and Brownian diffusion can reach a steady state within several tens of seconds, resulting in a localized concentration distribution described as $c = c_0 \exp(ST\Delta T)$.\textsuperscript{38,39} The exponential sensitivity of thermophoresis can afford precision measurement of biological process that leads to the change of $ST$.

Although dependent on a large number of factors in aqueous solutions, thermophoresis is essentially originated from the change in Gibbs free energy ($G$) of the solute-solvent system, which is predominately related with entropy of ionic shielding ($S_{ionic}$) and water hydration ($Shyd$) with simplified assumption of a constant pressure\textsuperscript{23}:

$$ST = -\frac{S_{ionic} + Shyd}{kT} = \frac{A}{kT} \left( \frac{\sigma_{eff}^2 \lambda_{DH} \beta}{4 \varepsilon_0 T} - \frac{Shyd}{kT} \right) \quad (1)$$

where $A$ is the surface area, $\sigma_{eff}$ is the effective charge density, $\lambda_{DH}$ is the Debye length, $\beta$ is the temperature derivative of permittivity, $\varepsilon$ is the dielectric constant, $\varepsilon_0$ is the permittivity of vacuum, and $k$ is the Boltzmann constant. Some temperature sensitive dyes, such as Rho-
damine B, could be used for temperature measurement within a microfluidic device.\textsuperscript{40} Equation (1) suggests the quadratic dependence of $S_T$ to size and has been confirmed for charged solid colloids (20 nm-2 μm).\textsuperscript{23,41} However, other studies observe a linear dependence of $S_T$ with size (11-253 nm).\textsuperscript{42} This inconsistency may result from the difficulty in controlling other affecting parameters for thermophoresis in experiments. For deformable nucleic acids and synthetic polymers, weak or vanishing size dependence has also been observed in a number of studies.\textsuperscript{43–45} Effective charge $\sigma_{\text{eff}}$ strongly influences the thermophoretic behavior ($S_T \propto \sigma_{\text{eff}}^2$) through its contribution to ionic shielding entropy. $S_T$ is also sensitive to the ionic strength which directly affects $\lambda_{DH}$,\textsuperscript{46} and a significant reduction of thermophoresis is seen in highly salty solutions.\textsuperscript{27,47,48} As $S_{\text{hydr}}$ in water increases with decreasing temperature and contributes to negative $S_T$, thermophoresis can become thermophilic at low ambient temperature (typically lower than room temperature) or high salt concentration ($\lambda_{DH} \sim 0$).\textsuperscript{23} Together, thermophoresis can be used for quantification of intermolecular interaction which often leads to change in size, effective charge, and hydration shell structure.

### 2.2 Coupling of thermophoresis and diffusiophoresis

Similar to thermophoresis, diffusiophoresis refers to a directed migration of particles along a gradient of solute concentration and has been used for effective transport of particles in microfluidics.\textsuperscript{49,50} Given its ability to create a steady concentration gradient, thermophoresis can be coupled with diffusiophoresis for precise particle manipulation and measurement (Figure 1B). Applying a temperature gradient to a polymer solution (typically polyethylene glycol, PEG) containing target particles, PEG molecules are depleted from the hot region to create a nonuniform distribution of PEG concentration. Due to the entropic repulsive interaction between PEG molecules and particle surfaces, the particles experience a net force directing towards the lower PEG concentration (the hot region), leading to an effective $S^*_T$ described as:\textsuperscript{28}

\begin{equation}
S^*_T = S^0_T - 2\pi \left( S_{T,\text{PEG}}^0 - \frac{1}{T} \right) a^2 \lambda^2 c_0 \tag{2}
\end{equation}

where $S^0_T$ is the intrinsic Soret coefficient of the target particles, $S_{T,\text{PEG}}^0$ is the Soret coefficient of PEG molecules, $a$ is the particle radius, $\lambda$ is the length scale of the repulsive interaction and is approximate to PEG size, and $c_0$ is the ambient PEG concentration. When $c_0$ is above a critical value (typically $\sim 2$ vol%), the diffusiophoresis induced by the PEG concentration gradient may overcome the intrinsic thermophoresis, reversing the particle migration from thermophobic to thermophilic. Owing to strong repulsive interaction at high PEG concentrations, a slight temperature rise (less than 10 K) created by laser irradiation is sufficient to achieve trapping of target particles irrespective of their own thermophoretic behaviors. The coupling of thermophoresis and diffusiophoresis allows for efficient manipulation and measurement of colloid/biomolecule systems, which has been demonstrated for synthetic polymer colloids,\textsuperscript{28} gold nanoparticles,\textsuperscript{51} DNAs,\textsuperscript{52} and RNAs\textsuperscript{52,53} in PEG solutions ($M_w$ of PEG = 6-10 KDa) with concentrations up to 15 vol%.

### 2.3 Coupling of thermophoresis and convection

In steady fluids, the range of thermophoresis is generally at the scale of several to tens of micrometers due to the fast thermal dissipation. By superimposing thermal convection on thermophoresis, molecules or particles in a large space (from millimeter to even macroscale) can be trapped and highly enriched (Figure 1C).\textsuperscript{54–56} Thermal convection in microfluidic devices can be generated mainly by two approaches: focusing an infrared (IR) laser beam into a thick fluid chamber (with a height of hundreds of micrometers)\textsuperscript{27,56} or exerting a horizontal temperature gradient in a vertically elongated capillary. In the former setup, the water around the core of microchamber exhibits the highest temperature rise. The buoyant force of the hot water core drives a toroidal convection that continuously shuttles particles toward the center of chamber bottom. Meanwhile, thermophoresis always repels particles away from the hot water core to achieve a stable balance with convection, leading to particle accumulation at the center of chamber bottom. The latter setup combines the circular convection flow with horizontal thermophoresis to enrich particles at the cold capillary bottom. The proper coupling of thermophoresis ($\propto a^2$) and convection ($\propto a$) can not only enable size-selective accumulation of biomolecules and bioparticles, but also provide thermal cycles for PCR-based DNA replication, suggesting a promising avenue for sensitive biological detection.\textsuperscript{5,32,57–59}

### 2.4 Coupling of thermophoresis and electric effects

In aqueous solutions, the surfaces of cells and colloids can be charged through ionization, adsorption, or chemical modification. The coupling of thermophoresis and accompanied electric effects have been exploited for
precision manipulation of cells and colloids. For example, applying a temperature gradient to an electrolyte solution can create an electric field when the positive and negative ions with different thermophoretic mobility are spatially separated (Figure 1D).29 This thermoelectric field exerts an electric force on the suspended cells or colloids and directs their migration toward the hot or cold region, which is determined by the sign of surface charge and direction of thermoelectric field. An effective strategy to create strong thermoelectric fields is to utilize a cationic surfactant, cetyltrimethylammonium chloride (CTAC), at a high concentration above critical micelle concentration (CMC).60 The self-assembled CTAC micelles surrounding by an electric double layer (EDL) display positive surface charges and a high thermophoretic mobility (∼10⁻¹¹ m²/K/s), which is one order of magnitude higher than that of individual Cl⁻ ions (∼10⁻¹² m²/K/s).60 Thus, CTAC micelles can be used to generate a strong thermoelectric field. In addition to the thermoelectric effect arising from the solvent body, electric effects at the particle-solvent interface under a temperature gradient can also be deployed for dynamic manipulation of cells and colloids.47,61 The water molecules in the EDL are highly orientated (low entropy) due to the polarization near the charged cell or colloid surface, showing a permittivity much lower than that in bulk water.62 Temperature perturbation contributes to the increase in the entropy of water molecules, resulting in a permittivity unbalance under a temperature gradient. A slip velocity directing toward the cold is generated around the cell/colloid surface and, thus, leads to the effective trapping of cells/colloids at the hot region.47,61

3 | BIOSENSING APPLICATIONS BY THERMOMICROFLUIDICS

3.1 | Detection of biomolecular interactions

Characterizing biomolecular interactions not only provides insights into bioprocesses in living systems, but also offers significant implications in drug development.26 Microscale thermophoresis technology (MST) has been used for quantifying biomolecular interactions in an immobilization-free, accurate manner, because the thermophoresis behavior of biomolecules is highly sensitive to the binding events (Figure 2A).63-65 MST involves the use of a glass capillary loaded with sample containing biomolecules with intrinsic or labeled fluorescence signals and binding ligands, followed by locally heating using IR laser (1480 nm) to generate a microscopic region of temperature elevation. Molecules depleted away from the hot region by thermophoresis form a steady local concentration distribution in approximately 10 s due to the balance between thermophoresis and thermal diffusion. Moreover, the binding of molecules and ligands results in the change of Sₚ, which also affects the concentration distribution of molecules. Using ligand titration experiments, MST can measure the binding affinity of proteins and other biomolecules in a wide range of media including selection buffer, PBS, cell extract, and blood plasma or serum.25

MST-based investigations of protein-protein interactions have revealed the roles of specific proteins in disease initiation and progression. For example, fibrous sheath interacting protein 1 (FSIP1) has been identified to bind (Kᵢ = 0.25-1.08 μM) to the intracellular domain of human epidermal growth factor receptor 2 (HER2) to enhance the invasiveness of HER2+ breast cancer.66 Besides, the binding of dimeric growth factor receptor-bound protein 2 (Grb2) to FGFR2 has implied a novel regulatory mechanism of RTK signaling by Grb2 in various cancer types.67 To facilitate the discovery of anticancer drugs, MST analyses have also been applied for screening of small molecules that exhibit high binding affinity to critical therapeutic protein targets, such as G-protein-coupled Rho guanine nucleotide exchange factors68 and pan-RAS proteins.69 In addition, measurements by MST have shown that endogenous small nucleolar RNAs (snoRNAs) can directly interact with Df31 protein to mediate RNA-chromatin networks, uncovering a conserved mechanism for chromatin structure regulation.70 In addition to MST, thermophoretic depletion has also been used for long-time monitoring of growth dynamics of single amyloid fibrils.71 Collectively, thermomicrofluidics becomes a powerful tool to measure biomolecular interactions.

3.2 | Concentration and replication of nucleic acids

Coupling of thermophoresis and diffusiophoresis inside microfluidic devices has been adapted to accumulate and separate nucleic acids (DNAs and RNAs) based on their overall length or stem structure.52,53 For instance, a DNA/RNA solution spiked with PEG (10 KDa) molecules is loaded into a 10-μm thick microchamber and heated by an IR laser (1480 nm) (Figure 2B). PEG molecules are thermophoretically depleted from the localized hot region to create a sharp concentration gradient. At moderate PEG concentrations (2.5 vol%), DNAs form a ring-like pattern upon the balance between thermophilic diffusiophoresis induced by PEG concentration gradient and their intrinsic thermophobic thermophoresis.52 For DNA length (N) up to 5.6 kbp, the ring radius (Rᵣ) monotonically decreases with N(Rᵣ ∝ N⁻⁰.₃), allowing for size-dependent
separation of DNAs in a manner similar to gel electrophoresis. In addition, RNAs can be separated in a stem-loop-dependent manner using PEG solution. RNAs with a long stem (such as ribozymes) have a high rigidity, which experience strong thermophilic diffusiophoresis to be accumulated at the hot region. Conversely, RNAs with a stem length less than 4 base pairs show intrinsic thermophoresis, which are depleted from the hot region.53

To enable simultaneous length selection and replication of oligonucleotides, an elongated vertical microcapillary is sandwiched by a Joule heating and a Peltier cooling element to induce a horizontal temperature difference between 94 and 61°C at the two sides.57 The synergetic effects of horizontal thermophoresis and descending thermal convection flow at the cold side contribute to the tight trapping of oligonucleotides at the capillary bottom by a factor of \(\exp(S_T)\).55 Meanwhile, the capillary is continuously fed with an upward flow of PCR buffer to shuttle short oligonucleotides (small \(S_T\)) out of the capillary, allowing for PCR replication of long ones (large \(S_T\)) by the convective thermal cycling.54 This scheme can be amended for point-of-care detection of pathogen nucleic acids by integrating isolation and concentration of
pathogens, thermal lysis, and PCR amplification within a single microfluidic device.

### 3.3 Profiling of extracellular vesicles (EVs)

Tumor-derived EVs (tEVs) are nano-/micrometer-sized lipid vesicles that contain proteins and nucleic acids of their parental tumor cells. Given their abundance and stability in peripheral blood, tEVs have been recognized as promising biomarkers for noninvasive tumor diagnosis and monitoring. Recently, an aptamer thermophoretic sensor has been developed to profile EV surface proteins in a rapid, sensitive, and cost-effective manner (Figure 2C). EVs are first labelled with Cy5-conjugated aptamers targeting tumor-related proteins, transferred to a 240-μm thick chamber, and locally heated by an IR laser (1480 nm) to generate a temperature gradient. The interplay of thermophoresis and convection leads to a size-dependent accumulation of EVs (>30 nm), whereas unbound aptamers and free proteins with small sizes (a few nm) remain dispersed due to their weak thermophoresis. As a result, the fluorescence intensity from aptamer-EV complexes can be significantly amplified, which is linearly correlated with expression level of target proteins on EVs. The obtained EV protein profiles are deciphered by supervised machine learning algorithms, allowing for automatic classification of different cancer types with an overall accuracy of approximately 70%. Moreover, the EV protein profile has a better performance than prostate-specific antigen blood test in distinguishing prostate cancer and benign prostate diseases, and assessment of biochemical recurrence after radical prostatectomy.

Recently, a thermophoresis-mediated DNA computation method has been developed for the detection of multiple protein markers on single EVs. Two breast cancer-associated proteins, EpCAM and HER2, were selected as the inputs of DNA-based AND gate. Two ssDNA strands containing aptamers targeting EpCAM and HER2, space sequences, and associative toehold activation sequences, were used to recognize the target proteins on EV membranes and to initiate the DNA computation. Subsequently, thermophoretic accumulation was applied to amplify the output signal of AND gate, allowing for precise identification of EVs derived from breast cancer cells. This method showed 97% accuracy for discrimination between breast cancer patients and healthy donors, and 90% accuracy to classify breast cancer with HER2+ or HER2− subtype.

The thermophoretic sensor has further been implemented with spherical nucleic acids (SNAs) for in situ detection of EV miRNAs without resorting to EV lysis, RNA extraction, and enzymatic amplification. SNAs (~18 nm in diameter) can be internalized by EVs through passive interaction with EV membranes. The target miRNA in EVs replaces the Cy5-conjugated DNA probes of SNAs, resulting in the fluorescence recovery. Consequently, thermophoretic enrichment of EVs loaded with SNAs amplifies the fluorescence signals, enabling sensitive profiling of EV miRNAs with a limit of detection of 0.36 fM. The EV miRNA profile indicates that the best marker, EV miR-375, can detect estrogen receptor-positive breast cancer at stage I-II with an accuracy of 85%.

### 3.4 Manipulation of cells and colloids

Surface charging behavior of cells and colloids in aqueous solutions is ubiquitous. The coupling of thermophoresis and electric effects in microfluidic devices can be used for precision manipulation of cells and colloids. For example, dynamic trapping of single cells is realized by thermophoretic tweezer that relies on a permittivity gradient at the cell-solvent interface induced by localized heating (Figure 2D). Cells are loaded into a 20 μm-thick microchamber with an Au-coated glass substrate, which can be locally heated upon the laser irradiation (532 nm). At the hot region, permittivity within the EDL of cell membranes has a sharp increase along the temperature gradient (~10^7 K/m), leading to a slip velocity directing from hot to cold. Therefore, cells with thermophilic thermophoresis can be trapped at the hot region. Using a computer-controlled digital micromirror device, multiple laser beams can be generated to achieve arbitrary spatial arrangement (such as linearity, circle, and matrix) of multiple cells (yeast and Escherichia coli cells) at a resolution of approximately 100 nm. The thermophoretic tweezer uses an optical power 100-1000 times lower than that of optical tweezer and the temperature rise is less than 10 K, suggesting great potential for characterizing cell-cell interactions and delivering target cells at single-cell level.

The thermoelectric effect has also been utilized for robust, versatile manipulation of colloids. The nanoparticle colloid suspension is spiked with a cationic surfactant, CTAC, at a concentration (i.e., 10 mM) above the CMC (0.13-0.16 mM). CTAC molecules can adsorb onto the surface of colloids to make them positively charged, and meanwhile CTAC molecules are self-assembled into micelles. Upon the laser-induced plasmonic heating, a local thermoelectric field leads to electrophoresis of charged colloids toward the hot region. Benefiting from the high spatial resolution of laser control, diverse metal nanocolloids (AuNT, AuNR, AuNS, and AgNS) can be either trapped at single-particle level for in situ darkfield spectroscopy measurement or assembled into electromagnetic “hot spots” for SERS sensing. By tuning...
bonding strength and length with various CTAC concentrations, this technique can precisely assemble colloids of diverse materials (metallic, dielectric, and polymeric) and sizes (200 nm to 2 μm) into 1D (chain), 2D (plane with different shapes), and even 3D configurations,78 showing great promise in the development of novel nanostructure-enhanced biosensing systems. In addition to laser heating, the Joule heating effect by using a silver-epoxy resistive heater could also induce a temperature gradient within a microfluidic device.36 The thermoelectric field stemming from the addition of specific electrolytes (such as NaOH and NaCl) strongly affected the thermophoresis behavior of polystyrene particles. The combination of thermophoresis and electrophoresis allowed for selective driving of particles toward the cold or the hot side when flowing through the microfluidic channel.

4 CONCLUSIONS
Thermomicrofluidics has been increasingly recognized as a promising tool for biosensing. Interrogating the thermophoresis behaviors in microspace has been used to analyze a wide range of biomolecular interactions (protein-protein and protein-nucleic acid) for fundamental and applied biomedical research. The combination of thermophoresis with other thermal-induced physical mechanisms, such as diffusiophoresis, convection, and electric effects, has shown great potential in precise manipulation and sensitive detection of various biomolecules and bioparticles including nucleic acids, EVs, and cells for disease diagnosis. The coupling of thermophoresis and diffusiophoresis has been realized by using PEG solutions. The fast thermal dissipation allows the coupling of thermophoresis and convection at the macroscale. The use of cationic surfactants can induce the coupling between thermophoresis and electrophoresis. Given the versatile, homogenous nature of thermomicrofluidics, further efforts can be made to integrate thermophoresis with other physical phenomena such as magnetic, acoustic, and inertial effects in a microfluidic system. To improve the clinical impact of thermomicrofluidics, multiplexed detection of a wide variety of biological analytes for real world applications is expected.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

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