Perspective

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Next-generation biomedical sensing through photoacoustic–electrochemical synergy

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Abstract: Modern biomedical sensing increasingly demands technologies capable of capturing structural, functional, and molecular information simultaneously. Photoacoustic (PA) and electrochemical (EC) sensing individually address these needs but exhibit inherent limitations when used alone. PA imaging offers deep-tissue, label-free visualization with high spatiotemporal resolution, yet lacks molecular specificity. Conversely, EC sensing provides quantitative, chemically specific information through electrode functionalization, but struggles with spatial mapping and noninvasive detection. Integrating these complementary modalities establishes a unified framework—Photoacoustic–Electrochemical Synergy (PAECS)—that fuses PA's noninvasive, flow-resolved optical contrast with EC's molecular selectivity and quantitative accuracy. PAECS enables multimodal sensing across scales, improving rare-event detection, dynamic monitoring of metabolic and hemodynamic processes, and mechanistic studies of disease and drug response. Applications include coupling PA flow cytometry with EC microfluidics for circulating tumor cell and biomarker analysis, as well as integrating PA imaging with EC metabolite monitoring for real-time tissue profiling. To realize PAECS, future efforts must address system co-registration, signal decoupling, and biomarker-driven design. By bridging optical, acoustic, and electrochemical information, PAECS represents a transformative step toward comprehensive, multiscale biomedical diagnostics and personalized health monitoring.

Keywords: photoacoustic–electrochemical synergy (PAECS); multimodal biosensing; in vivo molecular monitoring; photoacoustic flow cytometry; electrochemical microfluidics

1 The case for photoacoustic–electrochemical synergy (PAECS)

In the field of biomedical monitoring, there has been an increasing requirement for tools capable of capturing information across diverse biological scales without sacrificing sensitivity or specificity, and photoacoustic (PA) sensing and electrochemical (EC) sensing each fulfilled parts of this need yet they had complementary drawbacks.

EC sensors, based on functionalized electrodes, redox transduction, and impedance or amperometric readout schemes, offer direct molecular recognition with high sensitivity and low detection limits for small molecules, ions, metabolites, and protein markers [1–4]. They enable in vitro assays and have been adapted for in vivo or minimally invasive measurements. EC approaches face challenges in complex biological matrices (biofouling, interferents) [5], provide limited spatial information, and struggle to capture rare cells or transient events (e.g., circulating tumor cells [CTCs], typically present at 1–100 cells per mL in metastatic patients). PA-based techniques, such as PA imaging (PAI) and PA flow cytometry (PAFC), achieve non-invasive detection by generating ultrasound signals through light excitation of absorbers, whose intrinsic optical absorption and thermoelastic expansion properties endow them with excellent spatial resolution and penetration capability. It excels at label-free in vivo detection by leveraging endogenous and exogenous absorbers [6–8]. PA's strengths include deep-

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tissue penetration compared with purely optical methods and dynamic mapping of vascular and hemodynamic processes. However, PA readouts are typically limited to optical absorption signals, which may lack molecular specificity when chromophores overlap or target concentrations are low.

Integrating PA and EC modalities creates a unified sensing paradigm, which we term PAECS. In PAECS, PA provides noninvasive, flow-resolved contrast and label-free in vivo detection, while EC contributes molecular specificity, quantitative chemical analysis, and tunable surface functionalization. PAECS thus enriches signal content (optical, acoustic, electrochemical), improves rare-event detection, and enables applications spanning pharmacodynamics, disease mechanism studies, longitudinal monitoring, and holistic health-state assessment.

2 Why PA and EC belong together

PA and EC sensing are two highly complementary methods, with each having advantages in areas where the other has fundamental limitations. PA can offer non-invasive, high-resolution imaging with a high signal-to-noise ratio, has deep tissue penetrating capabilities, and is able to generate structural and functional maps of vasculature, oxygenation, and absorbing agents. Moreover, it's strong in monitoring the spatiotemporal aspects of dynamic in vivo processes like blood oxygen saturation, tumor microcirculation, and the movement of circulating cells by using optical absorption contrast. However, though it has these strong points, PA sensing usually gives readouts which mostly show optical absorption and this might be insufficient when trying to differentiate between multiple biomarkers with high molecular specificity.

EC sensing platforms show great flexibility as their detection targets could be easily adjusted by functionalizing electrodes with specific molecular recognition elements, which made it possible for EC sensors to detect a large variety of analytes ranging from small ions and metabolites to nucleic acids and proteins. Their shapes were highly flexible so that they could be put into wearable sweat sensors, subcutaneous probes for analyzing interstitial fluid, microfluidic chips or minimally invasive implants. These platforms were usually economical, could be easily miniaturized and enabled multiplexed detection while providing direct quantitative readings of chemical activity, but EC sensing failed to capture the spatial distribution patterns of analytes and often had difficulty in non-invasively detecting rare or transient circulating biomarkers.

A hopeful way ahead comes into being by integrating PA and EC sensing, which forms the PAECS framework (Figure 1), as techniques based on PA provide non-invasive, sensitive, and spatially resolved functional information to catch dynamic physiological processes in real time while EC sensors supply localized, chemically specific, and quantitative molecular data, so together they broaden the sensing scope from observing anatomy and physiology to resolving molecular-level chemistry and identity, creating new opportunities in pharmacology, personalized medicine, and long term health surveillance.

3 Where PAECS makes a difference

PAECS has great potential to push forward multiple biomedical frontiers as it showed how the coordinated use of PA and EC in this framework significantly widened the scope and improved the resolution of biomedical sensing and alike ideas had been probed in integrated ultrasound-EC sensors [9], which set up the possibility of connecting acoustic forms

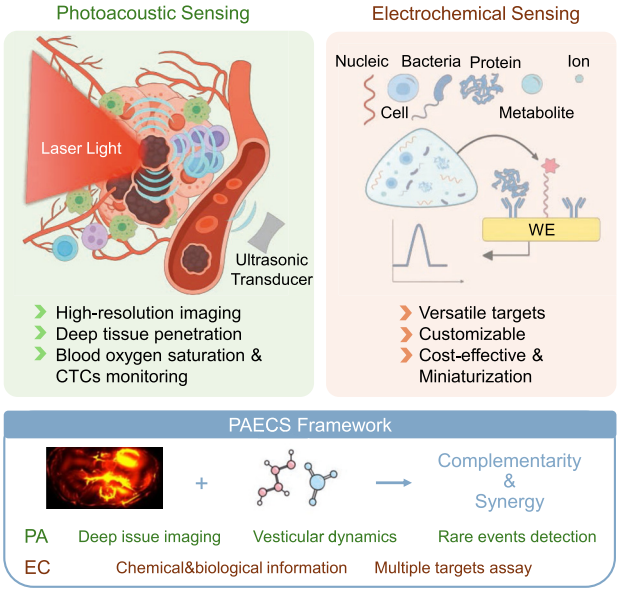

Figure 1: Conceptual schematic of the PAECS framework. The illustration highlights the integrative architecture of photoacoustic–electrochemical synergy (PAECS), wherein photoacoustic (PA) and electrochemical (EC) modalities converge to achieve multidimensional sensing across spatial, functional, and molecular scales. (Left) PA domain representing deep-tissue, dynamic, and label-free visualization of physiological and hemodynamic processes. (Right) EC domain depicting molecularly specific, quantitative, and surface-confined sensing of biochemical targets. (Bottom) PAECS integration illustrating cross-modal fusion of optical–acoustic and electrochemical readouts toward synergistic, multimodal biomedical monitoring.

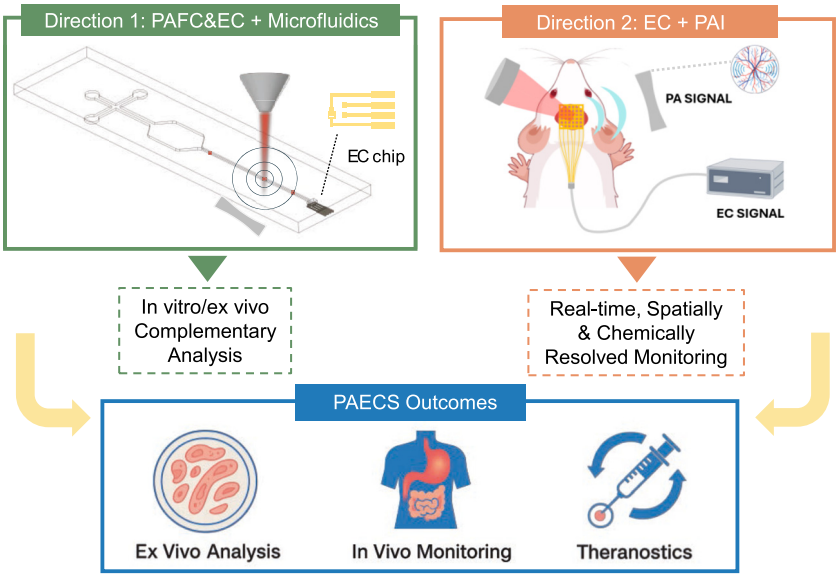

Figure 2: Emerging directions and applications within the PAECS framework.The figure summarizes two representative routes illustrating how photoacoustic–electrochemical synergy (PAECS) can be translated into practical biomedical platforms. (Left) Integration of photoacoustic flow cytometry (PAFC) with electrochemical (EC) microfluidic systems enables complementary in vitro and ex vivo analysis, combining label-free detection of rare circulating events with multiplexed biochemical profiling from small-volume samples. (Right) Coupling electrochemical sensing with photoacoustic imaging (PAI) establishes real-time, spatially and chemically resolved monitoring, linking molecular fluctuations with vascular and functional dynamics in living tissue. (Bottom) Directions highlight key PAECS outcomes, ranging from ex vivo biomarker analysis to in vivo monitoring and theranostic applications.

with electrochemistry. Following two ways demonstrate this potential:

(1) EC microfluidic platforms combined with PAFC.

Microfluidic EC chips allow for the detection of multiple biomarkers within complex fluids and the screening of panels consisting of cytokines, nucleic acids, or metabolites in samples as small as microliters thanks to their high throughput nature and the ability to customize electrode chemistries, making them potent instruments for comprehensive diagnostic purposes. However, solely relying on EC assays to detect ultra-rare occurrences like CTCs, which are frequently present at less than 100 cells per milliliter, remained difficult because random sampling might overlook these signals, but PAFC directly tackled this shortcoming by enabling label-free, in vivo detection of individual CTCs with great sensitivity [10] and in the workflow of photoacoustic endoscopy combined with PAECS, PAFC identified rare, valuable targets in vivo while microfluidic EC chips provided supplementary information regarding auxiliary biomarkers and chemical components from accessible biofluids.

(2) EC monitoring integrated with PAI.

More and more EC sensors are being designed with biocompatible and flexible substrates as well as customized surface chemistries, which makes it possible to continuously monitor metabolites, neurotransmitters, or therapeutic agents in various situations such as local tissue microenvironments, interstitial fluid through microneedles, and non-invasive skin-surface patches, and by combining PAI that shows the dynamics of vasculature and structures in deep tissue with real time electrochemical sensing, this multimodal platform allows for monitoring that is both spatially resolved and chemically specific at the same time, and such combination was helpful in correlating chemical differences with functional hemodynamic alterations, thus offering a deeper understanding of the mechanisms underlying disease progress and treatment outcomes (Figure 2), something that neither method could achieve on its own.

At their core, both routes are guided by a unified design rationale that systematically couples two modalities into an integrated sensing architecture, as illustrated in Figure 3. The interplay among physical signal generation, device co-optimization, and algorithmic fusion forms a dynamic feedback framework that synergistically enhances spatial resolution, molecular specificity, and quantitative accuracy across diverse biomedical contexts. Direction 1 focuses more on analytical precision through microfluidic chip integration and emphasizes dedicated target selection, calibration, and drift-free signal acquisition for quantitative biofluid analysis. In Direction 2, we highlight implantable system development, centering on device miniaturization, biocompatibility, and long-term stability for real-time, in vivo physiological monitoring.

4 What it will take to realize PAECS

Several challenges lay ahead in fusing the two techniques. After implanting or placing the EC chip, it would block laser

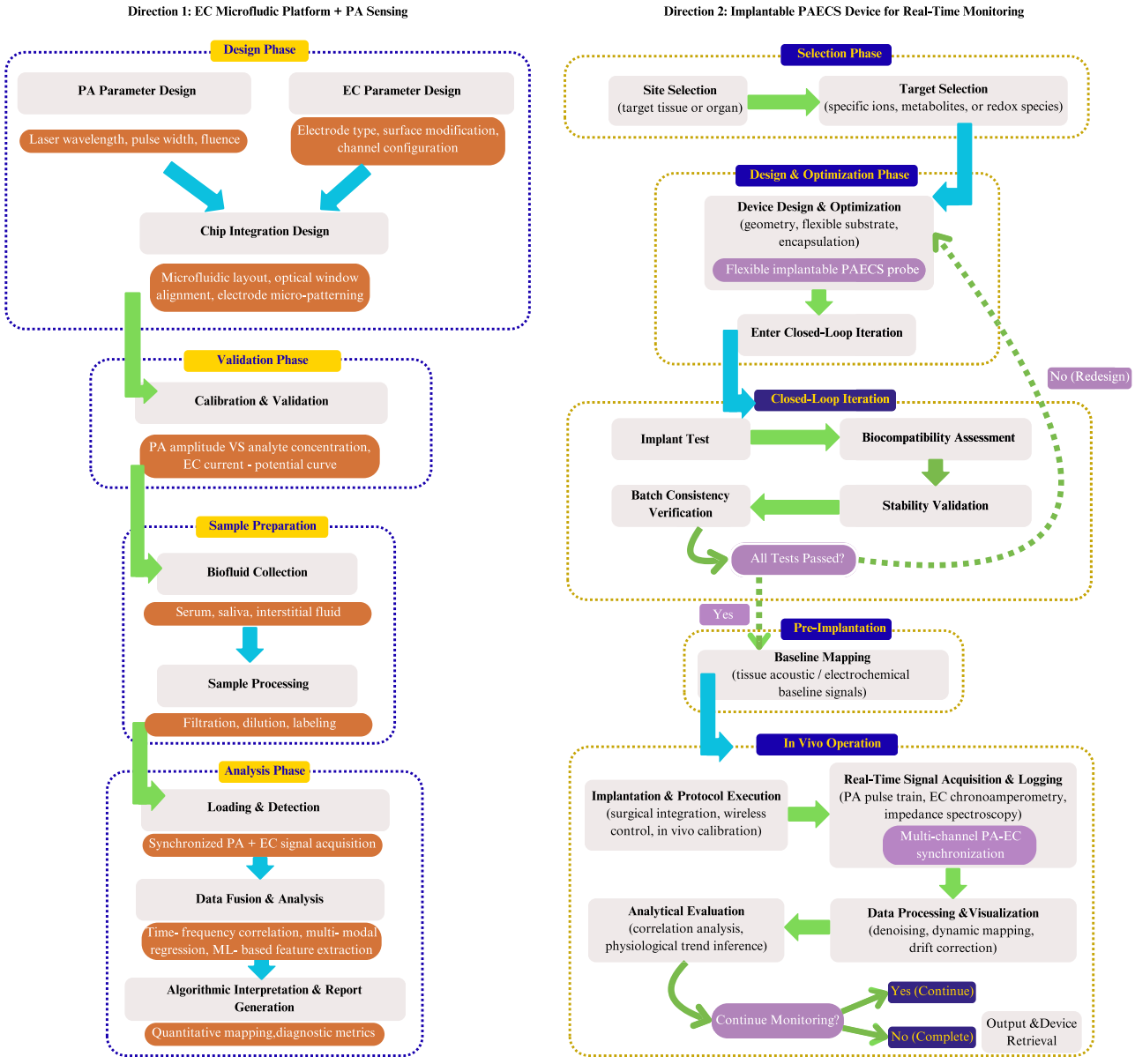

Figure 3: Workflow for two potential applications of PAECS. Direction 1 (left) outlines the development of an electrochemical (EC)–photoacoustic flow cytometry (PAFC) integrated chip for ex vivo micro-sample monitoring, while Direction 2 (right) depicts the system design for dual-modality in vivo monitoring.

and acoustic waves, thereby reducing the signal-to-noise ratio (SNR) and increasing artifacts. This necessitates specific requirements for the EC chip's transparency and geometric configuration. A series of breakthroughs and applications in flexible nanoelectronics have provided insights and solutions for achieving this goal [11]. In application scenarios, foreseeable performance improvements exist for multi-target ex vivo detection. However, for real-time monitoring, there is currently no clear approach that fully leverages information from both modalities to deliver clinical value. Vascular oxygenation patterns combined with local metabolic markers in tumors or ischemic areas could serve as a promising starting point [12].

Although PA and EC technologies have been individually firmly established for quite some time, the combination of these two through PAECS is expected to push sensing far beyond what is currently achievable, which would give rise to novel diagnostic, therapeutic, and research uses and by integrating structural, functional, and molecular chemical data on a single platform, PAECS offers distinct understanding of intricate biological systems. In order to turn this potential into practical instruments, future endeavors need

to coordinate device engineering with computational simulation, biomarker choice, and clinically relevant questions so as to close the distance between proof-of-concept research and actual biomedical influence in the real world.

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Use of Large Language Models, AI and Machine Learning Tools: The content, ideas, and interpretations are solely those of the authors.
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