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Molecular Recognition of Geraniol Using Electrochemical MIP Sensors: Fabrication, Characterization, and Translational Potential

DOCTORAL DISSERTATION

Natural Sciences,
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The dissertation was prepared between 2022 and 2026 at the State Research Institute Center for Physical Sciences and Technology.

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FIZINIŲ IR TECHNOLOGIJOS MOKSLŲ CENTRAS

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Geraniolio molekulinis atpažinimas naudojant elektrocheminius MIP jutiklius: gamyba, charakterizavimas ir transliacinis potencialas

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LIST OF PUBLICATIONS

The main findings of the doctoral thesis have been published in 6 review articles (R: 1-6), whereas the results have been published in 2 scientific publications (S: 1-2) and presented in 8 conference reports (C: 1–8).

Reviews

R:1 Kaspute G, Arunagiri BD, Alexander R, Ramanavicius A, Samukaite-Bubniene U. Development of Essential Oil Delivery Systems by 'Click Chemistry' Methods: Possible Ways to Manage Duchenne Muscular Dystrophy. *Materials*. 2023, *16*(19), 6537.
https://doi.org/10.3390/ma16196537

R:2 Kaspute G, Ramanavicius A, Prentice U. Molecular Imprinting Technology for Advanced Delivery of Essential Oils. *Polymers*. 2024, *16*(17), 2441.
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R:4 Kaspute G, Ivaskiene T, Ramanavicius A, Ramanavicius S, Prentice U. Terpenes and Essential Oils in Pharmaceutics: Applications as Therapeutic Agents and Penetration Enhancers with Advanced Delivery Systems for Improved Stability and Bioavailability. *Pharmaceutics.* 2025, *17*(6), 793.
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Scientific articles

S:1 Kaspute G, Plausinaitis D, Ratautaite V, Vaicekauskaite E, Bucinskas V, Ramanavicius A, Prentice U. (2025). Overcoming Template Surface Blocking: Geraniol Adsorption Studies Guiding MIP-Based Sensor Design. *International Journal of Molecular Sciences*. 2025, *26*(23), 11454. https://doi.org/10.3390/ijms262311454

S:2 Kaspute G, Plausinaitis D, Ratautaite V, Vaicekauskaite E, Ramanavicius A, Prentice U. A Comparative Study of Molecularly Imprinted Polypyrrole Architectures for Electrochemical Quartz Microbalance-Based Method Development for Geraniol Adsorption. *Polymers*. 2026, *18*(7), 804. https://doi.org/10.3390/polym18070804

LIST OF CO-AUTHORED SCIENTIFIC PUBLICATIONS WHICH ARE NOT PART OF THE DISSERTATION:

P:1 Kaspute G, Zebrauskas A, Prentice U. et al. The Integration of Robotics in Proactive Healthcare: Embracing Proactive Medicine for Enhanced Patient Care and Ethical Considerations. *Curr Robot Rep 2024*. https://doi.org/10.1007/s43154-024-00110-w

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P:3 Kaspute G, Bareikiene E, Prentice U, et al. A Comprehensive Review of Advanced Diagnostic Techniques for Endometriosis: New Approaches to Improving Women's Well-Being. *Medicina*, 2024, *60*, 1866. https://doi.org/10.3390/medicina60111866

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P:6 Alaburde S, Ivaska J, **Kaspute G**, Ivaskiene T. Impact of regulatory measures on the approval timelines of advanced therapy medicinal products by the European Medicines Agency. *Front Med (Lausanne)*, 2025, *12*, 1623689.
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LIST OF CONFERENCE PRESENTATIONS

C:1 **Kaspute G**, Prentice U. Poster presentation at the "Chemistry and Geosciences 2024" conference – *Essential oil chemistry from the geological standpoint: influence of biological effect*, Mar 22, 2024, Vilnius, Lithuania.

C:2 **Kaspute G**, Prentice U. Fiztech 2024 – *Essential oils as components of drug delivery systems*, Oct 15, 2024, Vilnius, Lithuania.

C:3 **Kaspute G**. Lithuanian Apitherapists Association Conference – *Perspectives of electrochemical sensor applications in apitherapy*, Dec 09, 2024, Vilnius, Lithuania. Award received for the presentation.

C:4 **Kaspute G**, Prentice U. Chemistry and Geosciences 2025 – *Sensing geraniol in essential oils using molecular imprinting techniques*, Mar 14, 2025, Vilnius, Lithuania.

C:5 **Kaspute G**, Prentice U. OpenReadings 2025 – *Translational approach of molecularly imprinted polymers integration with essential oils*, May 16, 2025, Vilnius, Lithuania.

C:6 Kaspute G, Prentice U. Grotthus 2025 – *Enhancing Molecularly Imprinted Polymer Sensor with Electrochemical Quartz Crystal Microbalance: Insights into Adsorption Dynamics and Sensor Optimization*, Jun 09, 2025, Vilnius, Lithuania.

OTHER CONFERENCE PRESENTATIONS

C:7 Kaspute G. Presentation at the *International Apitherapists Conference – Translational medicine: possibilities of apitherapy application*, Nov 12, 2022, Kaunas, Lithuania.

C:8 Kaspute G, Prentice U. Presentation at the conference *Thematic Cartography of Lithuania: from Past to Present – Geobotanical cartography: Time-sensitive challenges of interpretation*, Apr 18, 2024, Kaunas, Lithuania.

PARTICIPATION IN SCIENTIFIC SCHOOLS

Participation in the Winter School in Pavia, Dec 09 to Dec 16, 2023, under the topic *"Discovering the Unknown: AI in Healthcare, III Edition"*. During this Winter School, existing and emerging opportunities for applying artificial intelligence (AI) in healthcare were explored through lectures, networking, and the development of a project on AI use in early dementia diagnosis. The project considered ethical, social, economic, and business aspects, introduced the EU-funded "*Predictom*" innovation, and highlighted AI's potential for doctoral research, including applications in drug delivery systems and impact analysis.

Participation in the Summer School in Ljubljana, June 16–20, 2025, under the topic "*Summer School on Cell and Gene Therapies 2025*", organized within the *ADVANCE* program. This visit was significant for deepening knowledge of the development, application, and regulation of advanced therapy medicinal products (ATMPs). The acquired expertise is valuable for advancing interdisciplinary research in the application of electrochemical sensors and alternative formulations and is closely connected to my doctoral research on drug delivery systems.

ABBREVIATIONS

AFM	–	Atomic Force Microscopy
$\boldsymbol{C_{dl}}$	–	Double-layer capacitance
CPE	–	Constant Phase Element
CV	–	Cyclic Voltammetry
DAB	–	Dopamine Acrylamide-Based monomer
EGDMA	–	Ethylene Glycol Dimethacrylate
EIS	–	Electrochemical Impedance Spectroscopy
EOs	–	Essential Oils
MIP	–	Molecularly Imprinted Polymer
MIT	–	Molecular Imprinting Technique
NIP	–	Non-Imprinted Polymer
Ppy	–	Polypyrrole
QCM	–	Quartz Crystal Microbalance
$\boldsymbol{R_{ct}}$	–	Charge transfer resistance
TRM	–	Translational Readiness Model
TRL	–	Technology Readiness Level

1. LITERATURE REVIEW

1.1. Research Rationale and Scope

Increasing scientific interest in natural products and plant-derived compounds as potential therapeutic agents has led to a growing demand for reliable and robust analytical methods capable of detecting, characterizing, and monitoring these substances. Natural compounds are progressively recognized for their biological activity and potential applications in pharmaceutical, biomedical, and health-related fields. *Essential Oils* (EOs), as complex and highly concentrated natural mixtures, contain a wide range of biologically active constituents that contribute to their therapeutic properties [1]. These mixtures often exhibit antimicrobial, antioxidant, anti-inflammatory, and anticancer activities, which further emphasizes their importance in modern research and application [2–4]. As a result, the development of selective sensing systems targeting individual EOs components plays a crucial role in ensuring product quality, accurate dosage, and safe use.

Among the numerous constituents of EOs, geraniol has attracted considerable attention due to its wide range of biological and industrial applications. Geraniol is a naturally occurring monoterpenoid alcohol commonly found in rose (*Rosa rugosa*, *Rosa damascena*), citronella (*Cymbopogon winterianus*), palmarosa (*Cymbopogon martini*) and many other EOs [5]. It is widely used in the fragrance, cosmetic, and food industries because of its pleasant floral aroma. Beyond its sensory properties, geraniol demonstrates significant pharmacological activities, including antimicrobial, anti-inflammatory, antioxidant, and anticancer effects [6–9]. These properties make it a promising candidate for therapeutic applications as well as a valuable marker compound in quality control analysis.

In addition to pharmaceutical relevance, the analytical monitoring of natural compounds has gained importance in regulatory, environmental, and industrial contexts [10]. The increasing commercialization of plant-derived products, including EOs in cosmetics, nutraceuticals, and alternative medicine, has raised concerns regarding product authenticity, adulteration, and variability in composition [11]. These issues can directly affect product safety, efficacy, and consumer trust. Consequently, there is a strong demand for analytical tools that are not only accurate but also capable of rapid and selective detection. There is also increasing interest in developing methods that can be applied outside of specialized laboratory environments, enabling on-site analysis and real-time monitoring [12].

Conventional analytical techniques, such as gas chromatography and high-performance liquid chromatography, offer high sensitivity, precision, and reliability in the analysis of complex mixtures. These methods remain the gold standard for compound identification and quantification [13]. However, their practical application is often constrained by several factors, including high operational costs, bulky instrumentation, the need for skilled personnel, and time-consuming sample preparation procedures. These limitations restrict their use in field-based applications and routine quality control processes where rapid decision-making is usually required [14].

These challenges have stimulated interest in alternative sensing approaches that would provide simpler, faster, and more cost-effective solutions. Electrochemical sensing systems have emerged as promising candidates due to their inherent advantages, including high sensitivity, portability, low cost, and minimal sample preparation requirements [15]. Such systems also allow for real-time monitoring and can be adapted for miniaturized and point-of-care devices, making them highly attractive for applications in environmental monitoring, food safety, and pharmaceutical analysis [16].

Despite notable progress in analytical technologies, the development of selective, portable, and efficient sensing platforms for natural compounds remains a significant scientific challenge. One of the main difficulties lies in achieving sufficient selectivity when analyzing complex matrices that contain multiple structurally similar compounds [17]. Interference effects, signal overlap, and matrix complexity can compromise detection accuracy and reliability. At the same time, maintaining simplicity, affordability, and ease of operation is essential for practical implementation [18].

Addressing these challenges requires the integration of advanced materials, innovative sensor design, and optimized detection strategies. The continued development of electrochemical sensors tailored for specific target compounds, such as geraniol, represents an important step toward improving analytical performance while preserving operational simplicity. Such advancements have the potential to bridge the gap between laboratory-based analysis and real-world applications, supporting the broader use of natural products in science, industry, and healthcare.

1.2. Molecularly Imprinted Polymers in Analytical Applications

Recent progress in analytical chemistry has enabled the development of novel analytical systems based on synthetic receptors [19], with *Molecularly*

Imprinted Polymers (MIP) emerging as one of the most promising classes of materials [20–22]. These polymers have attracted widespread attention due to their ability to provide highly selective recognition while maintaining robustness under harsh chemical and physical conditions. MIP have been extensively explored in the design of electrochemical and optical biosensors for clinical diagnostics, environmental monitoring, and food safety applications. The growing demand for rapid, portable, and cost-effective diagnostic tools has further accelerated research into MIP-based sensing platforms [23]. The importance of advancing such technologies became evident following the COVID-19 pandemic, which exposed limitations in existing diagnostic systems and emphasized the need for reliable, scalable, and fast detection strategies [24,25].

Molecular Imprinting Technology (MIT) is based on the formation of artificial recognition sites within polymer matrices that are complementary to a target molecule in terms of the size, shape, and spatial arrangement of functional groups [26]. This biomimetic approach enables the creation of selective binding sites that resemble natural recognition elements, while overcoming many of their inherent limitations. These systems can be fabricated by using several imprinting strategies, including bulk imprinting, surface imprinting, and epitope imprinting [26]. Each approach offers distinct advantages depending on the size and nature of the target molecule, as well as the intended application of the sensor or separation system.

MIP function as synthetic analogues of biological receptors, such as antibodies and enzymes [27], providing comparable molecular recognition capabilities [28] while offering superior chemical and thermal stability [29]. Unlike biological receptors, MIP can be stored for extended periods without significant loss of activity, which makes them highly suitable for long-term and field-based applications [30,31]. During polymerization, functional monomers interact with a template molecule to form a pre-polymerization complex. After cross-linking and removal of the template, complementary binding cavities remain within the polymer structure, enabling selective molecular recognition [31]. This process results in the formation of "molecular memory" within the polymer, which is responsible for its selective recognition mechanism.

The selection of functional monomers is critical, as they determine the strength and nature of interactions with the target molecule. Common interactions include hydrogen bonding [32], electrostatic forces, and hydrophobic interactions [33]. Functional groups such as amines (NH_2), carboxylic acids (COOH), alcohols (OH), amides ($CONH_2$), and aromatic

rings (containing benzene groups) are frequently used to facilitate these interactions [33]. The rational design of monomer-template interactions is important for achieving high binding affinity and selectivity, and it often requires careful consideration of the physicochemical properties of both the monomer and the target analyte. The appropriate choice of a monomer therefore directly influences the analytical performance, sensitivity, and reproducibility of the resulting MIP system.

Cross-linkers, such as ethylene glycol dimethacrylate (EGDMA), 1,4-diaminobutane (DAB), and divinylbenzene (DVB), form stable three-dimensional polymer networks and define the rigidity and porosity of the material [34]. The degree of cross-linking also affects the accessibility of binding sites and the diffusion of analytes within the polymer matrix [35]. Solvents and porogenic agents play an essential role in shaping the pore structure and accessibility of binding sites [34] (Figure 1). Optimizing these parameters is crucial for ensuring efficient mass transfer and rapid binding kinetics in sensing applications.

MIP have been widely applied in diagnostics, biomarker detection, imaging, and drug delivery systems [36–40]. Their versatility allows them to be tailored for the recognition of a wide range of targets, including small organic molecules, proteins, and even whole cells. They are highly advantageous when analyzing complex biological matrices such as blood, urine, and saliva, where low analyte concentrations and interfering substances present significant analytical challenges [41]. Their high selectivity reduces matrix interference, enabling more accurate detection in real-world samples. In addition, MIP are increasingly utilized in extraction and sample preparation techniques, such as solid-phase extraction, where they offer enhanced selectivity, reusability, and cost efficiency [42]. These features make them attractive alternatives to conventional sorbent materials.

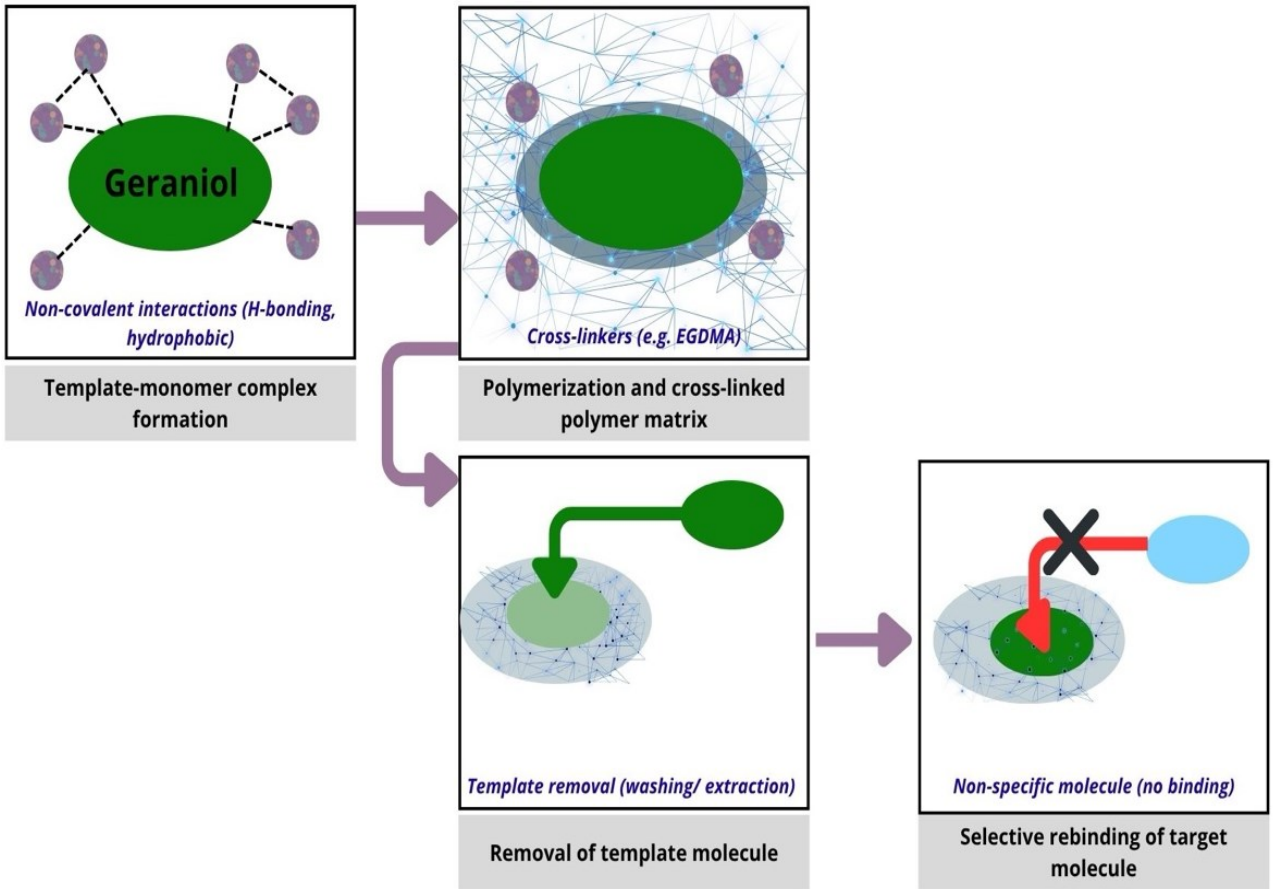

Figure 1. Schematic representation of the molecular imprinting process, including template–monomer complex formation, polymerization, template removal, and generation of selective recognition cavities

Molecular imprinting can be broadly classified into covalent, non-covalent, and semi-covalent approaches, depending on the nature of interactions between the template and functional monomers during polymerization [43]. Among these, non-covalent imprinting is the most widely used due to its simplicity and compatibility with a wide range of target molecules [44]. This method relies on reversible interactions, which simplifies template removal and rebinding processes. However, it may result in heterogeneous binding sites compared to covalent approaches, which offer more uniformity but are less versatile [44] (Figure 2). Semi-covalent approaches combine features of both strategies, thus offering a balance between binding site uniformity and synthetic versatility.

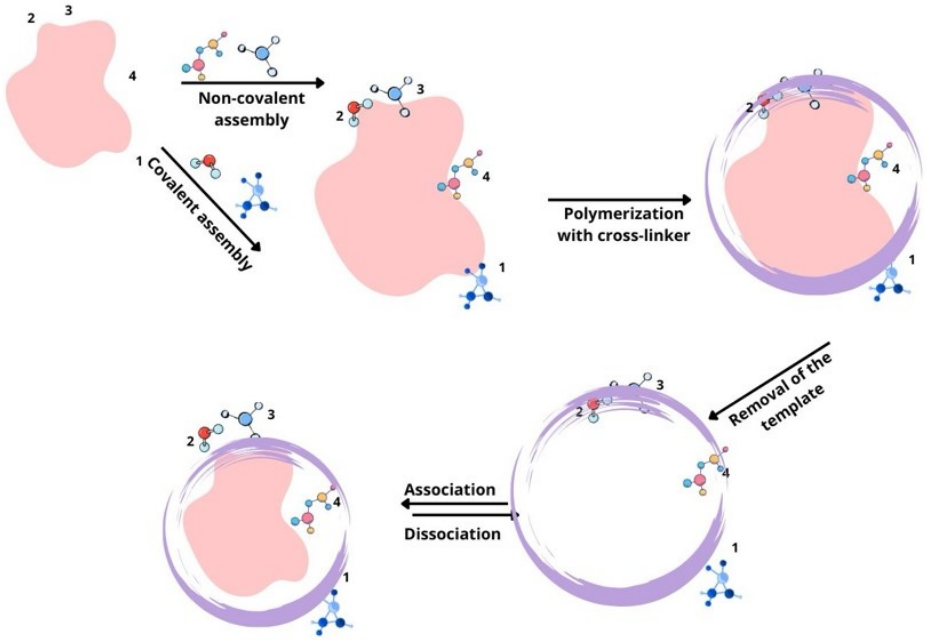

Figure 2. Schematic illustration of covalent and non-covalent molecular imprinting approaches [based on 43,45]

Surface imprinting techniques have gained increasing attention in sensor development, as they facilitate faster binding kinetics and improved accessibility of recognition sites compared to bulk-imprinted materials [44]. This approach involves creating imprinted sites on or near the surface of a substrate, which significantly reduces diffusion limitations and enhances the sensor response time. This is highly beneficial for large or structurally

complex molecules, where mass transfer within the polymer matrix can be a limiting factor [46]. As a result, surface-imprinted materials are widely used in the modern sensor design, where rapid detection and high sensitivity are required.

In recent years, the integration of MIP with transducer systems – such as electrochemical sensors, optical sensors, and piezoelectric devices – has expanded their application potential [47]. These hybrid systems combine the selectivity of MIP with the sensitivity of advanced detection methods, enabling the development of highly efficient sensing platforms [48].

Such integration has led to the creation of miniaturized, portable devices suitable for on-site analysis and real-time monitoring [50,51]. Furthermore, advances in nanomaterials and surface modification techniques have further enhanced the performance of MIP-based sensors by improving signal transduction, increasing the surface area, and facilitating electron transfer processes [51,52].

Despite these advances, several challenges remain in the development of MIP-based analytical systems. These include achieving uniform binding site distribution, improving sensitivity toward low-abundance analytes, and ensuring reproducibility across different batches of polymers [53]. Addressing these challenges requires continued research focused on material design, synthesis optimization, and the integration of novel functional components. The ongoing development of MIP technology is expected to play a significant role in the future of analytical science, supporting the creation of robust, selective, and accessible sensing systems for a wide range of applications.

1.3. Essential Oils as Analytical Targets

Essential oils are natural mixtures of volatile, lipophilic compounds derived from aromatic plants, typically containing 20–60 chemically diverse constituents [1]. These compounds, primarily monoterpenes and phenylpropanoids, contribute to the biological activity of EOs [2–4]. Due to this chemical diversity and biological activity, EOs have become increasingly relevant in modern scientific research, bridging the fields of pharmacology, analytical chemistry, and material science.

EOs have demonstrated effectiveness against both Gram-positive and Gram-negative bacteria , as well as potential antiviral activity through disruption of viral membranes [4,54]. They have also been investigated for applications in aromatherapy [55,56], insect control [57,58], and pharmaceutical formulations [59,60]. Their relevance has further increased with the growing demand for natural and plant-derived alternatives in

medicine and consumer products [61,62]. These characteristics make EOs both valuable and challenging analytical targets in the development of selective sensing and diagnostic platforms.

The importance of EOs in contemporary pharmaceutical and biomedical contexts is closely linked to the broader trend toward natural product-based drug discovery and development. Natural compounds are being increasingly explored as sources of bioactive molecules that can serve as templates or precursors for the development of new therapeutic agents [63]. EOs, as highly concentrated mixtures of biologically active compounds, provide a rich reservoir of such substances. Their composition allows for the delivery of potent chemical agents in relatively small quantities, which can be advantageous in acute therapeutic applications where rapid and effective biological responses are required [64].

At the same time, the use of EOs in clinical and non-clinical settings requires careful consideration of their composition and purity. In pharmaceutical applications, the presence of specific active compounds at controlled concentrations is critical for ensuring therapeutic efficacy and safety. Similarly, in aromatherapeutic and alternative medicine practices, the biological effects of EOs depend strongly on their chemical composition. The use of non-authentic, adulterated, or improperly processed EOs may lead to reduced effectiveness or even adverse health outcomes. Inaccurate composition can result in insufficient therapeutic action or unintended biological effects, ultimately compromising patient outcomes [65–67]. This highlights the importance of reliable analytical methods capable of verifying the authenticity and composition of EOs.

Despite their bioactivity, EOs present several analytical and formulation challenges. Their hydrophobic nature, volatility, and susceptibility to environmental factors such as light, heat, and oxygen lead to instability and degradation through oxidation, cyclization, and isomerization reactions [68]. These processes reduce the concentration of active compounds and may generate potentially harmful by-products. Such instability not only affects the shelf life of EOs-based products but also complicates their analytical characterization, as the composition may change over time or under different storage conditions [69].

The chemical composition of EOs can vary significantly depending on factors such as plant species, geographical origin, harvesting conditions, and extraction methods [70]. This variability complicates both analytical characterization and standardization, thus further emphasizing the need for selective detection of individual components rather than bulk analysis. Variations in composition can lead to inconsistencies in biological activity,

making it difficult to ensure reproducibility in both research and therapeutic applications. Furthermore, the complex and multicomponent nature of EOs limits their direct use as template systems in molecular imprinting, since high selectivity in MIP-based recognition typically requires a single, well-defined target molecule rather than a mixture of structurally diverse constituents [1].

From an analytical perspective, the presence of structurally similar compounds within EOs presents a major challenge for selective detection. Many terpenes and related compounds differ only slightly in functional groups or stereochemistry, which therefore requires highly selective recognition systems capable of distinguishing between closely related molecular structures [71,72]. This structural similarity often leads to cross-reactivity and interference in conventional analytical methods, thus reducing detection accuracy and reliability. These limitations strongly motivate the development of highly selective recognition platforms such as MIP for the discrimination of individual EOs constituents.

MIP offer a promising solution to many of these challenges by enabling the selective recognition of target compounds within complex mixtures. On the grounds of designing imprinting systems for specific EOs components, it becomes possible to isolate and monitor key bioactive molecules, thereby improving analytical precision and supporting quality control processes. This approach is highly relevant for ensuring the authenticity and safety of EOs-based products, as well as for optimizing their use in pharmaceutical and therapeutic applications.

Additionally, the lipophilic nature of EOs influences their interaction with biological membranes and sensor interfaces [73]. This property can enhance adsorption onto hydrophobic surfaces but may also lead to non-specific binding, which must be carefully controlled during sensor design. Non-specific interactions can significantly affect sensor selectivity and lead to false-positive signals, highlighting the importance of surface modification strategies and selective recognition elements in sensor development [74].

To improve stability and controlled handling of EOs components in various applications, different delivery systems have been developed, including nanoparticles, nanoemulsions, liposomes, and polymer-based carriers [43,60,75]. These systems enhance solubility [75], stability [68], and controlled release of EOs components through molecular interactions such as hydrogen bonding and hydrophobic interactions [76–79]. Such delivery systems also protect sensitive EOs constituents from environmental degradation, thereby preserving their biological activity and extending their functional lifetime. Polymeric systems, especially those based on biodegradable materials such as chitosan and polysaccharides, further support

improved handling and controlled interaction of EOs components in analytical and sensing contexts [52,80]. These materials are also compatible with MIT strategies, enabling the development of hybrid systems that combine controlled release with selective recognition.

Overall, the growing importance of EOs in modern science and industry, combined with their chemical complexity and variability, creates a strong need for advanced analytical approaches. The integration of selective recognition systems such as molecularly imprinted polymers with innovative sensing technologies provides a pathway toward overcoming current limitations. Such approaches enable precise detection, improved quality control, and safer application of essential oils across pharmaceutical, clinical, and industrial domains.

1.4. Geraniol as a Model Compound

Due to the complexity of EOs, the selection of a specific target molecule is necessary for the development of highly selective MIP. In this study, geraniol was chosen as the model compound. Geraniol was selected as a representative EOs constituent due to its relatively well-defined chemical structure and its occurrence in several clinically and industrially relevant EOs. Its presence across a wide range of EOs sources makes it a suitable marker compound for evaluating selective recognition systems within complex natural mixtures.

Geraniol is a naturally occurring terpene alcohol found in several EOs and is widely used in cosmetic and pharmaceutical applications due to its pleasant aroma and biological activity [81]. It exhibits antioxidant [5], anti-inflammatory [5], anticancer [6,7,9], and antibacterial properties [8,82], and has demonstrated potential in enhancing transdermal drug delivery [81]. These multifunctional properties contribute to its increasing relevance in both therapeutic and formulation sciences, where it is explored as an active compound as well as a functional additive. Importantly, geraniol has been extensively investigated in preclinical studies and widely considered a promising candidate for future clinical translation due to its demonstrated antimicrobial and anticancer activities.

As a representative EOs constituent, geraniol provides a suitable model for developing selective systems capable of distinguishing individual components within complex EOs matrices. This approach supports the development of selective sensing strategies for quality control, authentication, and safe application.

Structurally, geraniol is an acyclic monoterpene alcohol characterized by a flexible carbon chain and a terminal hydroxyl group [5]. This structural

flexibility may influence its orientation within the imprinted cavity, affecting binding affinity and selectivity. Therefore, the design of complementary binding sites must account for both functional group interactions and molecular conformation. From a molecular imprinting perspective, geraniol is well suited as a template molecule due to the presence of a hydroxyl functional group, which enables the formation of hydrogen bonds with functional monomers. These interactions facilitate the formation of stable pre-polymerization complexes [83], which are important for generating well-defined and selective binding cavities after template removal.

Another important consideration in the selection of geraniol is its physicochemical profile, which introduces additional experimental challenges. Geraniol is a lipophilic compound with very limited solubility in water [84]. During experimental work, it was observed to be poorly soluble even in commonly used organic solvents such as ethanol; consequently, it requires the use of alternative solvents, such as acetonitrile, to achieve sufficient dissolution. This limited solubility has important implications for both molecular imprinting and sensor development.

In electrochemical MIP-based systems, the solubility of the template molecule directly affects the preparation of the pre-polymerization mixture, the homogeneity of the polymer matrix, and the reproducibility of the imprinting process. Poor solubility may lead to aggregation or uneven distribution of the template within the polymer, resulting in non-uniform binding sites and a reduced sensor performance. Furthermore, in electrochemical sensing setups, the presence of poorly soluble or precipitating compounds can lead to practical issues such as blockage of microfluidic channels, fouling of electrode surfaces, or damage to pumping systems. These effects may compromise the stability and functionality of the sensor, turning solvent selection and system optimization into critical steps in the experimental design.

Therefore, when working with geraniol in MIP-based electrochemical systems, careful consideration must be given to solvent compatibility, system stability, and the prevention of clogging or deposition within the analytical setup. This highlights the importance of adapting both the imprinting protocol and the sensing environment to accommodate the physicochemical properties of the target analyte.

In addition, geraniol has closely related geometric isomers such as nerol, differing only in double bond configuration [85]. This structural similarity not only presents a challenge for selective recognition but also highlights the importance of precise imprinting conditions in the pursuit to achieve high discrimination between closely related analytes. The ability to

distinguish between such isomers is a critical parameter for evaluating the selectivity of MIP-based systems, as even minor structural differences can significantly influence biological activity and analytical outcomes (Figure 3).

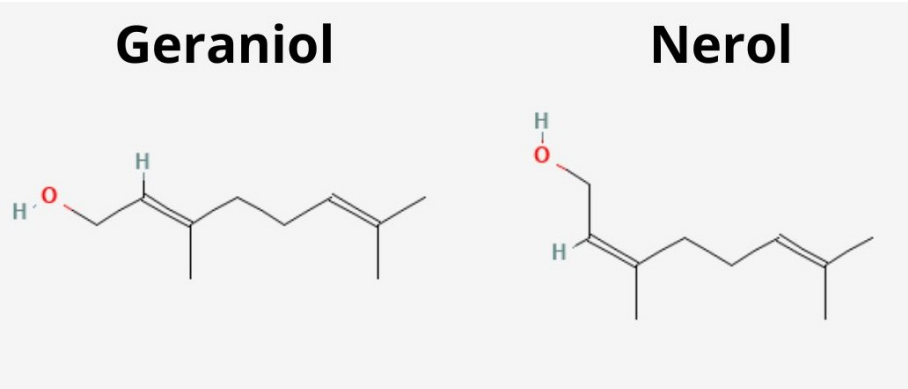

Figure 3. Chemical structures of geraniol and nerol

Other EOs constituents were not considered in this study due to their higher structural complexity, lower functional group accessibility, or reduced suitability for stable template–monomer interactions in MIP systems. Many EOs components lack functional groups capable of forming strong and directional interactions with monomers, which limits their applicability as effective template molecules. No alternative template molecules were evaluated in this study, and they were deemed to be beyond the scope of this research, as the objective was to develop and optimize a proof-of-concept MIP system while using a single representative EOs component.

Previous studies have demonstrated the feasibility of detecting geraniol by using MIP-based sensor systems. For example, a *Quartz Crystal Microbalance* (QCM)-based dual sensor array incorporating MIP technology successfully distinguished between citronellal and geraniol in citronella essential oil with high selectivity, as confirmed by principal component analysis (separability index: 38.996) [86]. In another study, a MIP synthesized by using geraniol as a template was applied onto a silver-electrode QCM via drop-casting, enabling sensitive and selective detection at ppm levels in palmarosa EOs, with performance comparable to gas chromatography methods [87]. These findings confirm the suitability of geraniol as a target analyte for selective sensing applications.

In addition to these studies, the use of geraniol as a model compound provides a practical balance between chemical simplicity and analytical relevance. Its structure is sufficiently simple to allow controlled imprinting, while still representing the challenges associated with EOs analysis, such as

structural similarity, hydrophobicity, and matrix complexity. This makes geraniol an ideal candidate for evaluating the performance of newly developed MIP-based sensing platforms.

Overall, the selection of geraniol as a model compound is justified by its biological relevance, widespread occurrence in essential oils, suitability for molecular imprinting, and its ability to represent key analytical challenges associated with EOs components. At the same time, its physicochemical properties, including low solubility and lipophilicity, introduce important practical considerations that must be addressed during sensor development. These combined factors make geraniol a highly appropriate and scientifically meaningful target for the development and optimization of selective MIP-based analytical systems.

1.5. Polymeric Materials and Pyrrole-Based Systems

Polymeric materials play a central role in molecular imprinting, drug delivery systems, and electrochemical sensing platforms due to their structural versatility and ability to provide controlled morphology, stability, and functional responsiveness [88]. Their physicochemical properties allow precise control over parameters such as porosity, surface area, mechanical strength, and chemical functionality, which are essential for designing high-performance analytical systems [89]. These characteristics support their use in selective sensing platforms [90].

Among polymeric materials, conducting polymers have gained significant attention in electrochemical sensing and molecular imprinting due to their unique combination of electrical conductivity and chemical functionality. Polypyrrole (Ppy) is one of the most widely studied conducting polymers which has been extensively applied in electrochemical sensors and MIP-based systems [91]. Its popularity is attributed to its straightforward synthesis, environmental stability, biocompatibility, and ability to form uniform films on a wide range of substrates. In addition, Ppy contains functional groups capable of interacting with template molecules through hydrogen bonding, electrostatic interactions, and π–π stacking, which are essential for the formation of stable and selective imprinting sites [51].

Ppy is well suited for molecular imprinting due to its ability to form conductive and stable polymer films via electrochemical polymerization. This process allows precise control over the film thickness, morphology, and deposition conditions, which are critical parameters in sensor fabrication [92]. Electropolymerization also enables localized deposition directly onto electrode surfaces, ensuring strong adhesion and uniform coating, which

enhances sensor reproducibility and performance. Furthermore, template molecules can be incorporated directly during electropolymerization, enabling the formation of molecularly imprinted polymer films directly on electrode surfaces without additional immobilization steps. This simplifies sensor fabrication and reduces potential sources of variability [93].

The intrinsic electrical conductivity of Ppy enables efficient transduction of molecular recognition events into measurable electrochemical signals, making it highly suitable for label-free sensing applications. Changes in conductivity, current, or impedance resulting from analyte binding can be directly correlated with analyte concentration, thus allowing sensitive and real-time detection [94]. This property is highly advantageous in the development of portable and miniaturized sensing devices.

Despite these advantages, Ppy is not the only monomer used in molecular imprinting systems. A wide range of functional monomers has been explored, each offering specific advantages and limitations depending on the target analyte and application. Commonly used monomers include methacrylic acid, acrylamide, styrene, aniline, and dopamine. These monomers differ in their functional groups, polymerization mechanisms, and interaction capabilities, which directly influence the performance of the resulting MIP.

Methacrylic acid is one of the most frequently used monomers in traditional MIP synthesis due to its ability to form strong hydrogen bonds with a variety of template molecules [95]. It is widely applied in bulk polymerization methods and provides good selectivity for small organic molecules. However, methacrylic acid-based polymers are typically non-conductive, which limits their direct application in electrochemical sensing without additional modification or incorporation of conductive materials [32,96,97].

Acrylamide is another commonly used monomer which forms stable hydrogen-bonding interactions and is suitable for imprinting polar compounds. It offers good flexibility in polymer design but may suffer from lower selectivity in aqueous environments due to competition with solvent molecules [98,99]. Similarly, styrene-based polymers provide hydrophobic interactions and structural rigidity but lack functional diversity and conductivity, which can restrict their application in sensing platforms [100].

Conducting polymers – such as polyaniline and polydopamine – have also been explored as alternatives to Ppy. Polyaniline offers good electrical conductivity and environmental stability, but its polymerization process is more sensitive to pH conditions, which can complicate synthesis and reproducibility [101,102]. Polydopamine, on the other hand, is known for its

strong adhesion properties and ability to form thin coatings on various substrates. It also supports multiple interaction mechanisms, including hydrogen bonding and π–π interactions [103]. However, its conductivity is lower compared to Ppy, which may limit signal transduction efficiency in electrochemical applications.

Compared to these alternatives, Ppy provides a practically preferable balance of conductivity, chemical stability, functional versatility, and controllable electropolymerization, making it suitable for MIP-based electrochemical sensors.

Polymeric systems can be tailored in terms of chemical composition, structure, and functionality to optimize porosity, mechanical stability, and responsiveness to environmental stimuli, which are key parameters for enhancing selectivity and performance in molecularly imprinted sensor platforms [104]. In the context of EOs analysis, the choice of a polymer is especially critical due to the hydrophobic nature and structural diversity of target analytes. The polymer matrix must provide sufficient interaction strength while maintaining the accessibility of binding sites and compatibility with the sensing environment.

The selection of pyrrole as the functional monomer in this study is therefore based on several considerations. First, its ability to undergo electropolymerization enables direct fabrication of MIP films on electrode surfaces, simplifying the overall sensor design. Second, its conductive nature allows efficient signal transduction without the need for additional conductive modifiers. Third, its functional groups support multiple interaction mechanisms with target molecules such as geraniol, facilitating the formation of stable and selective binding sites.

Moreover, pyrrole-based systems are well suited for integration with electrochemical detection methods, which are central to this work. The combination of molecular imprinting and conductive polymer matrices enables the development of highly sensitive, selective, and portable sensing platforms capable of operating in complex environments. While alternative monomers may offer stronger or more specific interactions in certain cases, they often require more complex fabrication procedures or lack the conductivity needed for direct electrochemical sensing. Therefore, pyrrole represents a practical and effective choice for developing MIP-based sensors targeting essential oil components.

Overall, polymeric materials remain a fundamental component in the design of molecularly imprinted systems. The careful selection of monomers and polymerization strategies is essential for achieving optimal performance. Pyrrole-based systems, in this context, provide a versatile and efficient

platform that balances the ease of fabrication, functional performance, and compatibility with electrochemical sensing technologies.

1.6. Conceptual Development of the Sensor System

Following the establishment of the research rationale and the selection of geraniol as the target compound, the study progressed toward the conceptual development of a sensor system capable of selective molecular recognition. The design of this system was guided by the need to address the analytical challenges associated with EOs components, including low aqueous solubility, structural similarity between the analytes, and the requirement for selective detection in complex matrices.

Electrochemical sensing techniques were selected because they are compatible with surface-modified electrodes and allow sensitive monitoring of interfacial recognition events [105]. Among the available electrochemical methods, *Cyclic Voltammetry* (CV) and *Electrochemical Impedance Spectroscopy* (EIS) were considered, with EIS serving as the primary transduction technique for evaluating changes in interfacial properties associated with analyte binding.

In this context, variations in charge transfer resistance and interfacial capacitance provide a direct measure of molecular recognition events occurring at the MIP interface, enabling sensitive and label-free detection of geraniol. This approach is advantageous because it does not require additional labelling steps or complex signal amplification strategies, thereby simplifying the analytical procedure and reducing potential sources of error.

Given the physicochemical properties of geraniol discussed above, including its limited solubility and lipophilic nature, careful optimization of the electrochemical environment was necessary. The use of suitable solvent systems and supporting electrolytes was considered essential to ensure stable signal acquisition while preventing issues such as electrode fouling or blockage of fluidic components. This consideration directly influenced the design of the experimental setup and the selection of the operating conditions for electrochemical measurements.

To complement the electrochemical measurements, QCM was employed as a secondary technique to monitor mass changes at the sensor surface in real time. QCM measurements provide quantitative information on polymer deposition and analyte adsorption processes, thereby supporting the evaluation of the imprinting efficiency and the binding mechanism [106]. This technique enables the detection of nanogram-level mass variations, offering

high sensitivity for monitoring both film formation and analyte interaction dynamics.

Surface characterization was further performed by using *Atomic Force Microscopy* (AFM) as a supporting structural analysis technique. AFM enables detailed assessment of surface morphology, roughness, and uniformity of the deposited polymer films, which are critical parameters influencing the binding site accessibility as well as the overall sensor performance [107]. The ability to visualize nanoscale surface features provides valuable insight into the quality of the imprinted polymer layer and helps identify structural factors that may affect sensor reproducibility and sensitivity.

The combined application of electrochemical impedance spectroscopy, QCM, and AFM provides a complementary and hierarchical framework for the development and evaluation of MIP-based sensor systems. In this integrated approach, EIS acts as the primary functional readout, where changes in charge transfer resistance (R_t) and interfacial capacitance are used to monitor variations in electron transfer kinetics associated with analyte binding at the MIP interface [108]. QCM provides independent validation of mass-related processes by monitoring frequency shifts associated with polymer deposition and analyte adsorption at the sensor interface [109]. AFM provides additional insight into the structural properties of the sensing interface by elucidating the surface morphology, roughness, and the organization of the polymer layers formed during film deposition.

This multi-technique approach enables a comprehensive understanding of the relationships between the material structure, film formation, and sensing performance. By combining these techniques, it becomes possible to correlate physicochemical properties of the sensing layer with its functional response, thereby improving the interpretation of experimental results. Correlating morphological information obtained from AFM with electrochemical response data from EIS allows for a detailed assessment of how surface characteristics influence the analyte recognition efficiency. Similarly, QCM measurements offer independent confirmation of mass changes associated with polymer formation and binding events, thereby increasing the robustness and reliability of the overall sensor characterization.

The integration of these analytical methods also supports the identification of potential limitations in sensor performance, such as non-specific binding, incomplete template removal, or structural heterogeneity of the polymer layer. Addressing these factors is essential for optimizing sensor sensitivity, selectivity, and reproducibility.

Together, these complementary techniques provide cross-validated evidence that strengthens the interpretation of interfacial processes occurring within the sensing layers. Ultimately, this integrated methodology supports a more reliable structure–function analysis, which is essential for optimizing MIP-based sensor design. This systematic approach ensures that both material properties and analytical performance are evaluated in a coordinated manner, contributing to the development of a robust and reliable sensing platform for the detection of geraniol and related compounds.

1.7. Translational Potential and Sensor System Implementation

While the conceptual design and laboratory validation of MIP-based sensor systems demonstrate promising analytical performance, the transition from laboratory-scale prototypes to real-world applications remains a significant challenge [110]. Many sensors developed under controlled experimental conditions do not progress beyond the prototype stage, primarily due to limitations related to device integration, environmental stability, and scalability [111]. This gap between scientific innovation and practical implementation is commonly described within the framework of translational research.

The term ‘translation’ in a scientific context refers to the process of transforming fundamental research findings into practical applications that can be used in clinical, industrial, or field settings [112]. In biomedical sciences, translational research is often described as a multi-stage process that bridges the gap between laboratory discoveries (‘bench’) and real-world use (‘bedside’ or ‘field’) [113]. This concept gained significant importance in the late 20^{th} and early 21^{st} centuries, as it became evident that many promising technologies failed to reach practical application despite strong experimental performance [116]. The growing emphasis on translational pathways reflects the need to ensure that scientific advancements lead to tangible societal and technological benefits [114].

In the context of sensor development, translation involves several critical steps beyond the initial proof-of-concept validation. These include optimization of sensitivity and selectivity, reproducibility across multiple fabrication batches, validation in real and complex sample matrices, device miniaturization, and integration into user-friendly platforms. Each of these stages introduces new challenges that are not typically addressed in early-stage laboratory studies.

For practical implementation, the developed QCM-MIP sensor requires integration with compact and portable electronic instrumentation.

Miniaturized potentiostat/galvanostat systems are essential for enabling electrochemical readout in non-laboratory environments, thus supporting potential adaptation into field-deployable or handheld analytical devices. Such integration represents a key step in translating sensor technology from an experimental setup to a usable analytical tool.

The pathway toward commercialization typically involves sequential stages, including proof-of-concept validation, optimization of sensor performance and reproducibility, testing in complex real sample matrices, device miniaturization, and, finally, system integration and scale-up for production [16]. For the present system, a critical next step involves validation in real essential oil matrices, where matrix effects and interfering compounds may influence the sensor response. This step is important because real samples introduce variability that cannot be fully replicated under controlled laboratory conditions.

From a technological perspective, advances in microelectronics and embedded systems have enabled the development of low-power, portable potentiostat platforms that can be directly integrated with electrochemical and QCM-based sensors [115,116]. The incorporation of wireless communication modules such as Bluetooth or Wi-Fi further enhance functionality by enabling real-time data acquisition and remote monitoring [117,118]. These developments support the creation of smart sensing systems that can operate in decentralized environments, which is increasingly important for applications in environmental monitoring, healthcare, and industrial quality control.

Environmental factors represent a key consideration for real-world deployment. Variations in temperature, pH, humidity, and co-existing compounds can significantly affect polymer stability, binding kinetics, and sensor response [119]. Temperature-dependent changes in polymer structure and binding interactions may influence the performance of the MIP layer, necessitating systematic stability evaluation under operational conditions [120]. Long-term stability and resistance to environmental fluctuations are crucial criteria for ensuring consistent sensor performance outside laboratory conditions. From an economic standpoint, MIP-based systems offer advantages due to their low-cost synthesis and chemical stability compared to biological recognition elements [121]. However, the overall system cost is largely determined by electronic integration, device packaging, and scalability of fabrication methods [122]. This highlights the importance of designing sensor systems with both material efficiency and manufacturing feasibility in mind. The use of commercially available electronic components and scalable

fabrication strategies is therefore essential for achieving cost-effective implementation.

Despite extensive research on MIP-based sensors, relatively few systems have reached commercialization. Numerous studies have demonstrated highly selective and sensitive detection of target analytes using MIP-based platforms, including applications in biomarker detection [38,123,124], environmental monitoring [51,103,125], and food analysis [126–128]. However, these systems often remain at the proof-of-concept stage due to challenges related to reproducibility, standardization, and integration into fully functional devices. This situation illustrates the broader issue within translational research, where scientific feasibility does not always translate into practical applicability.

Examples of MIP-based sensing systems that have shown strong laboratory performance but have not yet been commercialized include sensors for pharmaceutical compounds, pesticides, and volatile organic compounds. In many cases, these systems demonstrate excellent selectivity under controlled conditions but face limitations when exposed to complex real-world targets or long-term operational conditions.

In the case of EOs analysis, several studies have reported the development of MIP-based sensors targeting specific EOs constituents, including geraniol and structurally related compounds [114,129]. For instance, research has demonstrated the use of MIP-coated QCM systems capable of distinguishing geraniol from similar terpenes with high selectivity. These systems showed promising analytical performance, including sensitivity at low concentration levels and the ability to differentiate structurally similar molecules [129]. However, such sensors remain at the experimental stage, and have not yet been translated into commercially available devices or routinely used analytical tools.

The lack of commercialization is often associated with challenges such as limited robustness under variable environmental conditions, difficulties in scaling up fabrication processes, and the need for integrated electronic and data-processing systems. Additionally, regulatory requirements and validation standards for analytical devices can further slow down the transition from research to application [130].

Overall, the developed QCM-MIP sensor for geraniol represents a robust proof-of-concept platform. However, further work is required to bridge the gap between laboratory validation and practical application. This requires further validation under practical EOs analysis conditions. Addressing these challenges will be key to advancing the translational potential of MIP-based

sensing technologies and enabling their broader adoption in industrial, environmental, and clinical settings.

1.8. Limitations and Future Perspectives

Despite s lengthy list of their advantages, MIP-based sensors still face several challenges, when applied to complex matrices such as EOs [131]. One of the main limitations is the achievement of high selectivity in the presence of structurally similar compounds, such as monoterpene isomers, which can interfere with target recognition and reduce analytical specificity [132].

In addition, while the developed QCM-MIP system for geraniol demonstrates promising performance under controlled conditions, its application to real samples requires further evaluation of matrix effects, including the influence of co-existing EOs components on the binding behavior and signal response. Improvement of sensitivity and lowering of detection limits remain important objectives for enabling reliable detection in diluted or complex real-world samples [132].

Environmental factors such as temperature, pH, and interfering substances may further influence sensor performance by affecting polymer stability, binding kinetics, and analyte–receptor interactions [125]. These effects are relevant for field-deployable applications and require systematic stability assessment under operational conditions [133].

Another important limitation is sensor surface fouling, which may occur during analysis of complex organic matrices and can lead to reduced sensitivity and reproducibility over time [134]. Addressing this issue will require the development of regeneration protocols or disposable sensing formats, depending on the intended application.

Long-term stability and storage conditions of MIP-based sensors also remain critical considerations for practical deployment, particularly in portable or point-of-care systems where consistent performance over time is required [135].

An additional critical limitation of MIP technology is the potential for incomplete template removal and template leakage. Residual template molecules trapped within the polymer matrix may lead to false-positive signals or overestimation of analyte concentration, thereby affecting analytical accuracy [136]. Similarly, leaching of template residues during operation can compromise signal stability and reproducibility. This issue is especially relevant when dealing with hydrophobic and strongly interacting compounds such as geraniol, where removal from the polymer network can be more challenging [137].

Another key challenge is the lack of standardization in MIP synthesis and characterization protocols. Variations in polymerization conditions, monomer-to-template ratios, and fabrication methods often result in batch-to-batch variability, which limits reproducibility between laboratories. This variability represents a major barrier to the broader adoption of MIP-based sensors in regulated analytical environments [138].

Advances in these areas could contribute to an improved quality control of natural products and the detection of adulterated or falsified materials.

From a technological perspective, future development should focus on the integration of MIP-based sensing layers with miniaturized and portable instrumentation. The use of low power potentiostat/galvanostat systems, screen-printed electrodes, and compact QCM platforms represents a key step toward real-world implementation. These developments would enable transition from laboratory-based measurements to field-deployable analytical devices [139].

In parallel, advances in data processing and communication technologies, including wireless data transfer and digital signal analysis, may further enhance usability by enabling real-time monitoring and remote data interpretation. However, such approaches should be implemented in a targeted manner, while ensuring compatibility with the specific sensing mechanism rather than introducing unnecessary system complexity.

Another important direction involves the development of multi-analyte sensing platforms and sensor arrays, often referred to as ‘electronic noses’ or ‘electronic tongues’, which are capable of analyzing complex mixtures such as EOs [126]. These systems rely on pattern recognition rather than single-analyte detection and are promising for applications in food quality control, environmental monitoring, and pharmaceutical analysis.

From a materials perspective, ongoing research is directed toward improving the performance of MIPs through advanced fabrication strategies, including nanostructured materials, hybrid composites, and surface-imprinted layers with an enhanced binding site accessibility [140]. These developments aim to overcome limitations related to slow binding kinetics and incomplete template removal. The incorporation of conductive nanomaterials and hierarchical porous structures has been shown to significantly increase the effective surface area and improve mass transport within the polymer matrix. Such approaches also enhance signal transduction efficiency, leading to faster response times and an improved analytical sensitivity.

A further future direction involves improving the standardization and regulatory validation of MIP-based sensors. For real-world deployment, especially in pharmaceutical or clinical contexts, robust validation against

established analytical methods such as gas chromatography and high-performance liquid chromatography is required. This comparative validation is essential for demonstrating accuracy, reliability, and regulatory acceptance.

Additionally, the performance of MIP-based systems should be benchmarked against biological recognition elements such as antibodies and enzymes. While MIPs offer superior stability, they still often lag biological systems in terms of absolute selectivity and affinity. Bridging this performance gap through hybrid materials or biomimetic strategies represents a promising research direction.

Despite these advances, the translation of sensor technologies into commercially viable products remains limited. Future research should therefore focus on improving reproducibility, environmental robustness, and practical implementation. In this context, the development of MIP-based electrochemical sensors for specific natural compounds, such as geraniol, represents a promising contribution to the field, when combined with portable instrumentation and integrated data analysis systems.

1.9. Research Hypothesis and Tasks

The aim of this study is to develop and investigate molecularly imprinted Ppy (MIP) layers on electrochemical sensor surfaces for the selective recognition of geraniol, with a particular focus on understanding the role of geraniol–electrode interactions in the formation, structure, and sensing performance of the polymeric system.

To test this hypothesis, the following tasks were defined:

1. To investigate the adsorption mechanism of geraniol on gold sensor surfaces and evaluate its influence on polymer layer formation.
2. To develop and optimize molecularly imprinted Ppy layers by using electrochemical polymerization.
3. To characterize the morphology and structural properties of the developed polymer layers by using AFM.
4. To evaluate the performance of the developed system as a prototype electrochemical sensing platform for geraniol detection and assess its potential for practical applications.

Statements for Defense

1. Geraniol adsorption on gold electrodes alters the electrochemical polymerization behavior of pyrrole and directly influences the

structural organization, interfacial properties, and growth dynamics of molecularly imprinted Ppy layers.

2. The dual-layer NIP/MIP architecture significantly enhances adsorption capacity and interfacial restructuring, producing approximately 25-fold higher adsorbed mass (~602 ng vs. ~24 ng) and a stronger decrease in double-layer capacitance (~2.5-fold) compared to single-layer systems.
3. QCM and EIS analyses demonstrate that geraniol adsorption in the developed MIP systems is diffusion-controlled and partially irreversible, involving both surface binding and penetration into the polymer network, with estimated surface densities reaching ~10^{16} molecules·cm^{-2}.
4. AFM analysis confirms the formation of continuous and morphologically distinct polymer films, while the developed electrochemical MIP platform provides selective geraniol recognition in essential-oil-related systems and demonstrates applicability for sensing hydrophobic fragrance compounds.

Scientific Novelty

The scientific novelty of this work lies in the elucidation of the geraniol–Ppy interaction mechanism and its influence on the formation of molecularly imprinted polymer layers in electrochemical systems. Although dual-layer MIP/NIP architectures and Ppy-based electrochemical sensors have already been investigated in previous studies, this work introduces several original aspects related to the target analyte selection, sensing strategy, and mechanistic understanding of polymer formation.

In particular, the sensor was specifically designed for the detection of EOs components, namely, geraniol, which remains a relatively unexplored target in electrochemical molecular imprinting systems. Analysis of the available literature and scientific databases indicates that electrochemical MIP sensors for geraniol are still very limited, primarily due to the challenges associated with detecting hydrophobic EOs compounds that exhibit poor solubility in aqueous media and are typically analyzed in organic solvent systems. These limitations reduce the practical transferability of conventional sensing approaches and make the development of selective sensing platforms for such analytes particularly challenging.

The choice of geraniol as a target molecule is also significant from a regulatory and toxicological perspective. In recent years, geraniol has gained increasing attention because it has been included among the regulated

fragrance allergens relevant to aromatherapy and cosmetic formulations under European Union (EU) cosmetic legislation. According to current EU regulations, fragrance allergens such as geraniol must be individually declared on cosmetic product labels when their concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products. Furthermore, recent amendments to EU Regulation 1223/2009 have expanded the list of regulated fragrance allergens from 26 to more than 80 substances, which reflects the increasing regulatory attention toward sensitizing fragrance compounds.

Compared with more commonly investigated compounds such as menthol, geraniol remains considerably less explored in electrochemical sensing applications despite its growing toxicological and industrial relevance. One of the main reasons is the limited transferability of sensing systems for essential oil compounds, which are often poorly soluble in aqueous media and require organic solvent environments. This creates additional challenges for molecular imprinting and electrochemical detection. Therefore, the development of selective sensing platforms for geraniol represents both an analytical and technological challenge with an increasing practical importance.

It has already been demonstrated that geraniol not only adsorbs onto the gold electrode surface but also actively influences the kinetics of pyrrole electrochemical polymerization. This leads to a direct modification of the structure, growth rate, and organization of the resulting MIP layer. These findings indicate that the template molecule is not merely a passive imprinting agent but also an active structural factor that shapes polymer formation during electropolymerization.

Furthermore, a dual-layer NIP/MIP architecture has been proposed and experimentally validated, showing a improved electrode–polymer interface stability, reduced structural defects, and an enhanced reproducibility of the sensing layer compared to conventional single-layer systems.

In addition, an integrated characterization approach combining CV, EIS, QCM, and AFM has been developed. This multimodal methodology enables comprehensive evaluation of electrochemical processes, mass changes, and surface morphology during MIP formation.

Overall, the results provide new insight into the dual role of small organic molecules such as geraniol, which act not only as target analytes but also as active structural modulators in molecular imprinting processes, thereby influencing the functional properties of sensing materials.

2. MATERIALS AND METHODS

2.1. Materials and Chemicals

Pyrrole (98%, *Alfa Aesar*, Karlsruhe, Germany) was distilled prior to use for the preparation of MIP. Geraniol (*Sigma-Aldrich*, Burlington, MA, USA) and acetonitrile (*Carl Roth GmbH & Co.*, Karlsruhe, Germany) were used as received. Lithium perchlorate ($LiClO_4$, *ThermoFisher*, Erlangen, Germany) served as the supporting electrolyte for electrochemical measurements. First-grade freshly distilled water (resistivity: 0.055 µS/cm at 25 °C) was used in all aqueous solutions. Ammonium hydroxide solution (25%, pure p.a., CAS No: 1336-21-6, Poland) and hydrogen peroxide (≥30%, p.a., CAS No: 7722-84-1, Slovakia) were used for sensor regeneration and cleaning procedures (Figure 4).

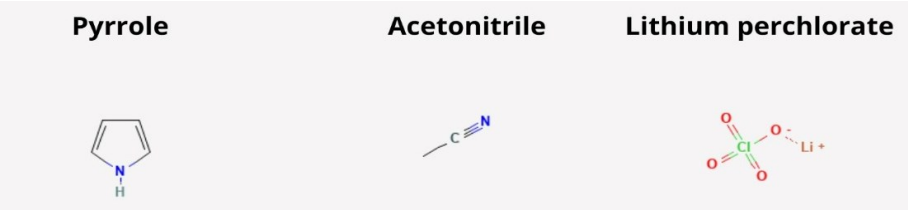

Figure 4. Chemical structure of pyrrole, acetonitrile and lithium perchlorate

2.2. Instrumentation

Electrochemical measurements were carried out by using two potentiostat/galvanostat systems: a Metrohm AutoLAB µAutolab III/FRA2 (µ3AUT71079, controlled by NOVA 2.1.3 software, *EcoChemie*, The Netherlands) and a *Gamry Echem Analyst* (version 5.30, USA). Liquid handling and flow administration for QCM experiments were achieved with a binary HP 1100 HPLC pump (model G1312A, *Hewlett-Packard*, Germany), and sample switching was controlled by using a six-channel, two-position *Rheodyne* valve (USA).

A 5 MHz electrochemical quartz crystal microbalance (QCM) sensor (QSX 301, *Biolin Scientific*, Sweden) with a gold-coated working electrode (surface area S = 0.79 cm^2, acoustically active area 0.20 cm^2) was used to monitor polymer deposition and template interactions in real time. The sensor was mounted in a custom 3D-printed flow cell (working volume: 350 µL) and connected to an oscillator circuit controlled by a *Maxtek RQCM* device. All QCM measurements were performed under continuous flow at 0.5–1 mL/min at ambient temperature.

Electrochemical experiments were performed in a three-electrode configuration, with the gold-coated QCM sensor as the working electrode, a platinum counter electrode, and an Ag/AgCl reference electrode. *Cyclic Voltammetry* (CV) and *Electrochemical Impedance Spectroscopy* (EIS) were employed to monitor polymer formation, redox behavior, and template interactions.

2.3. Preparation of Solutions

A series of solutions was prepared for the fabrication of MIP and non-imprinted polymer (NIP) films, as well as for electrochemical and QCM measurements. All solutions were based on a mixed solvent system of acetonitrile and distilled water containing 0.1 mol/L $LiClO_4$ as a supporting electrolyte.

Solution I consisted of 0.1 mol/L $LiClO_4$ in (50:50 v/v) acetonitrile/water and was used as the base electrolyte for all electrochemical experiments.

Solution II contained 0.05 mol/L pyrrole dissolved in Solution I and was used for the electropolymerization of NIP films and for the formation of the first layer in double-layer MIP structures.

Solution III contained 0.05 mol/L pyrrole and 0.005 mol/L geraniol in Solution I and was used for the electropolymerization of MIP films, with geraniol acting as the template molecule.

For QCM experiments, a separate solvent system was used. **QCM Solution A** consisted of a 50:50 (v/v) mixture of acetonitrile and water and was used to establish baseline frequency stability. **QCM Solution B** contained 0.05 mol/L geraniol in Solution A and was used for adsorption measurements.

2.4. Experimental Systems

Two experimental setups were used in this study. The first system was used for electrochemical measurements, including CV and EIS, performed on a gold (Au) electrode. These measurements were used to optimize experimental conditions and to evaluate electrode behavior in the selected electrolyte systems. The second system was based on QCM measurements and was used for monitoring mass changes during polymer formation and analyte adsorption.

Different solvent systems were used depending on the analytical technique. For electrochemical measurements, $LiClO_4$ was included as a supporting electrolyte so that to ensure sufficient ionic conductivity. For QCM measurements, a mixed acetonitrile/water solvent system was used to maintain geraniol solubility while ensuring stable frequency measurements and minimizing solvent-related effects on the sensor response. This systematic

separation of solvent conditions allowed each technique to operate under its optimal physicochemical environment, while improving the reliability and comparability of the obtained results.

The experimental workflow is presented in Figure 5.

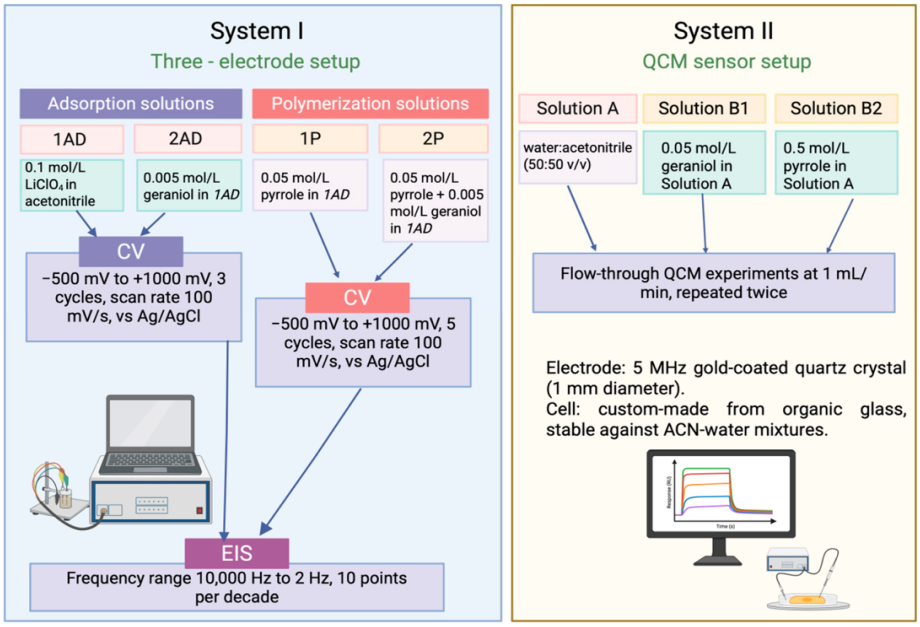

Figure 5. Schematic representation of system development and applied analytical methods [137]

All experiments were performed at least in duplicate so that to ensure reproducibility. In cases where higher variability was observed, additional measurements were carried out to confirm consistency of the results. The reported data therefore represent averaged values, thus providing a more reliable assessment of experimental trends and minimizing the influence of random experimental error. This approach ensures that the observed effects can be attributed to the behavior of the material under investigation rather than measurement uncertainty.

2.5. Pre-Treatment of Gold Working Electrodes

Prior to polymer deposition, electrodes were pre-treated so that to ensure clean, reproducible surfaces. Electrochemical cleaning was performed in 0.1 mol/L $LiClO_4$ by cycling the potential between –500 mV and +1000 mV vs. Ag/AgCl at a sweep rate of 100 mV/s. The number of cycles ranged from 3 to

10 depending on the application, and cleaning continued until a stable CV response was observed. This procedure removed adsorbed contaminants and prepared the electrode for electropolymerization.

2.6. Adsorption Experiments

Adsorption experiments were performed by using two complementary systems: (i) a classical three-electrode electrochemical setup (System I) and (ii) a QCM sensor system (System II).

Both systems were used to investigate geraniol adsorption and MIP formation under controlled conditions (Table 1).

Table 1. Definitions of the two-electrode systems used in the experiment [137]

	System I – Classical Three-Electrode Setup	**System II – QCM Sensor Setup**
Electrodes	Working electrode: gold disk electrode (1 mm diameter). Reference electrode: Ag/AgCl (3 M KCl). Counter electrode: Pt disk electrode (2 mm diameter).	Electrode: 5 MHz gold-coated quartz crystal (1 mm diameter). Cell: custom-made from organic glass, stable against acetonitrile–water mixtures.
Solutions	Adsorption solutions: 1AD: 0.1 mol/L acetonitrile with $LiClO_4$ (supporting electrolyte). 2AD: 0.005 mol/L geraniol in 1AD. Polymerization solutions: 1P: 0.05 mol/L pyrrole in 1AD. 2P: 0.05 mol/L pyrrole + 0.005 mol/L geraniol in 1AD.	Neutral solution A: water: acetonitrile (50:50 *v*/*v*), used as baseline. Solution B1: 0.05 mol/L geraniol in solution A. Solution B2: 0.5 mol/L pyrrole in solution A.
Techniques	CV, CA and EIS.	QCM
Techniques conditions	CV: In 1AD and 2AD: −500 mV to +1000 mV, 3 cycles, scan rate 100 mV/s, vs. Ag/AgCl. In 1P and 2P: −500 mV to +1000 mV, 5 cycles, scan rate 100 mV/s, vs. Ag/AgCl, max current 0.2 mA. EIS: frequency range 10,000 Hz → 2 Hz, 10 points per decade.	Flow-through QCM experiments at 1 mL/min, repeated twice.

2.7. Fabrication of Geraniol-Imprinted Polypyrrole Films

Geraniol-imprinted polypyrrole (Ppy-MIP) films were electropolymerized on gold-coated QCM sensors by using CV. Three architectures were prepared, as presented below:

1. **Single-layer MIP:** Polymerization with Solution III.
2. **Double-layer MIP:** A NIP pyrrole layer was first deposited by using Solution II, followed by Solution III.
3. **Non-imprinted polymer (NIP):** Polymerization by using Solution II.

QCM discs were selected as substrates because they provide a well-defined gold surface suitable for reproducible functionalization and, simultaneously, represent a platform directly compatible with mass-sensitive and electrochemical sensing architectures. Thus, the chosen substrate reflects the intended final sensor configuration rather than serving solely as a model surface.

The number of cycles was chosen upon considering the need to achieve mechanically stable films rather than identical thicknesses. Electropolymerization was synchronized with QCM measurements to correlate mass deposition with applied potentials (Table 2).

Table 2. Steps and parameters of MIP/NIP formation [132]

Step No.	Single-Layer MIP	Double-Layer MIP	NIP
1	CV using solution I performed over a potential window of −500 to +1000 mV, repeated for four cycles at a sweep rate of 100 mV/s.		
2	Polymerization using solution III was conducted within a range from −500 mV to +850 mV, with a scan rate of 50 mV/s, and a total of 8 cycles, to ensure polymer layer growth while capturing film formation dynamics.	Polymerization was implemented in two steps: Solution II: −500 and +850 mV, scan rate of 50 mV/s, and 7 cycles. Solution III: −500 mV to +850 mV, a scan rate of 50 mV/s, and 5 cycles.	Polymerization using solution II was conducted between −500 and +850 mV, at a scan rate of 50 mV/s, with 7 cycles at the same sweep rate, to ensure polymer layer growth while capturing film formation dynamics.

2.8. Template Extraction

Following electropolymerization, geraniol was removed from the MIP layers by immersion in a 1:1 (v/v) mixture of acetonitrile and water under gentle

agitation for a fixed time. Electrodes were then rinsed with distilled water and dried under ambient conditions prior to characterization.

2.9. Gold Sensor Regeneration

After experiments, gold-coated QCM sensors were regenerated by using a piranha solution (60:40 v/v ammonium hydroxide 25%: hydrogen peroxide ≥30%) for 3–5 minutes depending on the prior experiment. Sensors were then rinsed three times with distilled water, dried naturally, and stored in a 50:50 water-acetonitrile mixture until further use. All experiments were repeated at least twice to ensure reproducibility.

2.10. Atomic Force Microscopy Characterization

AFM measurements were performed with the objective to investigate the nanoscale surface morphology of bare gold substrates (QCM disks), Ppy-NIP films, and Ppy-MIP films before and after template extraction. AFM imaging was carried out in the tapping mode under ambient conditions while using silicon cantilevers with a nominal tip radius of <10 nm. Scan areas ranging from 1 × 1 μm² to 5 × 5 μm² were recorded at a fixed scan rate. Height and phase images were collected simultaneously.

Surface roughness parameters (root-mean-square roughness, R_a/R_q) and height distributions were extracted from the AFM topography data by using standard image analysis software *Gwyddion*. All samples were imaged at multiple locations in order to confirm surface homogeneity and reproducibility.

AFM was selected for surface analysis because it enables nanometer-scale evaluation of topography and roughness without additional conductive coatings or vacuum treatment. This allows examination of the functionalized surface in its native state. Moreover, AFM-derived morphological parameters have been shown in my previous studies [132,137] to correlate with interfacial electrochemical stability, making AFM an appropriate and reliable method to validate the surface preparation quality.

3. RESULTS AND DISCUSSION

3.1. Adsorption Mechanism of Geraniol on the Sensor Surface

Adsorption is a surface phenomenon in which molecules from a liquid or gas phase accumulate at the interface of a solid material due to intermolecular interactions [141]. In electrochemical and sensor systems, adsorption plays a crucial role because it directly determines how analytes interact with electrode surfaces prior to any electrochemical reaction [142] or polymer formation [143].

Depending on the nature of interactions, adsorption can be physical (physisorption, governed by weak van der Waals forces) or chemical (chemisorption, involving stronger specific interactions such as hydrogen bonding, coordination, or electron transfer). Adsorption may occur via physisorption, governed by weak intermolecular forces such as van der Waals and hydrophobic interactions [144], or chemisorption, involving stronger specific interactions such as hydrogen bonding or charge transfer [145]. In electrochemical systems, physisorption typically dominates initial surface accumulation, while chemisorption contributes to stronger and more stable surface binding.

Understanding adsorption is crucial for MIP systems, as template–surface interactions directly influence polymer growth, binding site formation, and the overall sensor performance. If adsorption is too weak, template molecules may fail to be retained long enough to influence polymer formation. If it is too strong, they may block active sites or disrupt monomer organization. Therefore, an optimal adsorption balance is required to ensure controlled imprint formation and uniform binding site generation [137,146]. Therefore, adsorption is not only a preliminary characterization step but also a key factor in rational sensor design.

The adsorption behavior of geraniol on gold electrodes has been investigated to evaluate its suitability as a template molecule. Electrochemical and QCM measurements demonstrated that geraniol exhibits a measurable and persistent adsorption affinity toward the gold surface [137]. This indicates that geraniol does not remain fully solvated in the bulk solution but instead forms an interfacial layer at the electrode surface prior to polymerization. From a molecular perspective, geraniol is a lipophilic monoterpene alcohol containing a terminal hydroxyl group. Its adsorption on gold is likely governed by a combination of hydrophobic interactions between the carbon chain and the surface, as well as weak coordination or dipole interactions involving the hydroxyl group. Although Au is relatively inert, it can support weak

adsorption through polarization effects and surface electron density redistribution. For comparison, pyrrole adsorption was also evaluated, as pyrrole is the monomer responsible for Ppy formation during electropolymerization. Pyrrole is known to adsorb efficiently onto conductive surfaces prior to oxidation, forming an initial monomer layer which facilitates nucleation and polymer growth [147] (Figure 6).

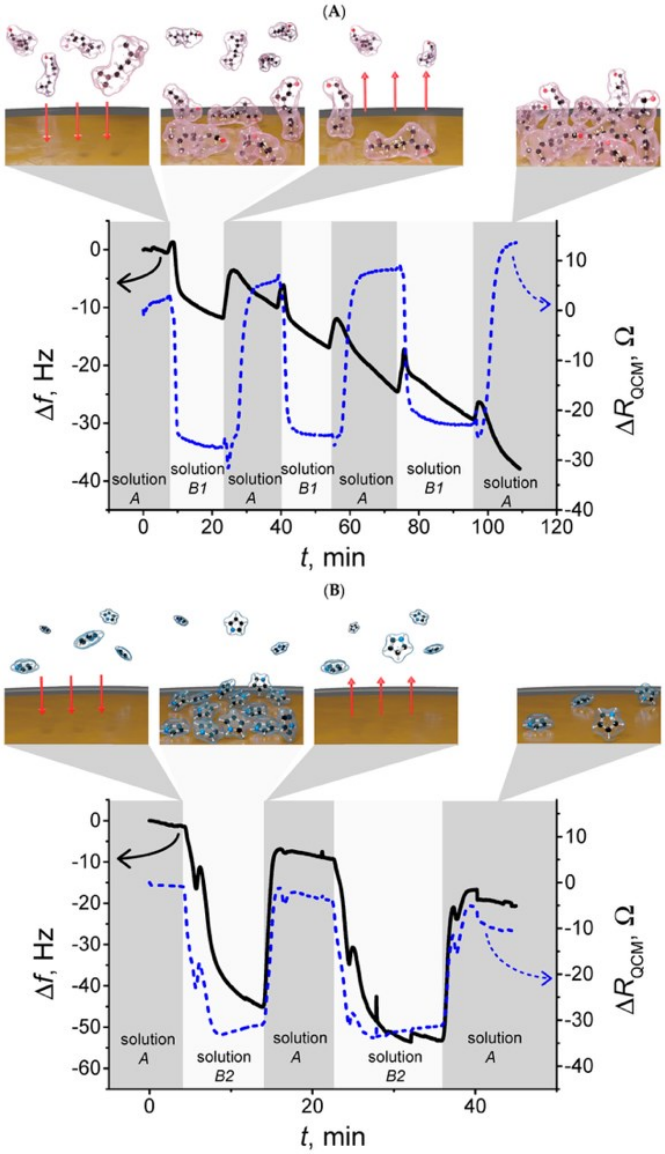

Figure 6. Adsorption of 0.05 mol/L geraniol (B1) and 0.5 mol/L pyrrole (B2) on Au electrode compared to baseline solution A (flow rate 1 mL/min, two cycles). The red arrows indicate adsorption and desorption phases [137]

This adsorption step is essential for establishing a uniform conductive polymer film and controlling polymer growth kinetics**.**

When both geraniol and pyrrole are present simultaneously, a competitive adsorption process is observed. Geraniol occupies a significant fraction of active surface sites on the gold electrode, thereby reducing the effective adsorption of pyrrole. This phenomenon corresponds to competitive surface adsorption, where multiple species compete for the same energetic adsorption sites based on their relative affinity, concentration, and surface interaction strength [148].

Mechanistically, this competition leads to a dynamic equilibrium at the electrode interface. Geraniol, due to its hydrophobic character and surface affinity, can pre-adsorb onto gold and partially block adsorption sites that would otherwise be available for pyrrole. As a result, pyrrole adsorption becomes spatially restricted, leading to reduced and non-uniform nucleation of Ppy. This directly affects polymer growth kinetics, resulting in heterogeneous film formation and altered interfacial morphology.

From the perspective of molecular imprinting, this effect is highly significant. Non-uniform monomer distribution during polymerization leads to variability in binding cavity formation, which may affect both selectivity and reproducibility of the final MIP layer. Therefore, understanding competitive adsorption is essential for predicting and controlling the imprinting efficiency.

The adsorption behavior of such systems can be quantitatively described by using adsorption isotherm models. The most used models are the Langmuir and Freundlich isotherms [149].

The Langmuir isotherm assumes monolayer adsorption on a homogeneous surface with a finite number of identical binding sites and no interaction between adsorbed species [149]. It is mathematically expressed as:

$$\theta = \frac{K_L C}{1+K_L C} \quad (1)$$

where θ is the fractional surface coverage, C is the analyte concentration, and K_L is the Langmuir adsorption constant. This model is useful for describing an idealized adsorption mechanism and estimating binding affinity under equilibrium conditions.

The Freundlich isotherm, in contrast, is an empirical model used to describe adsorption on heterogeneous surfaces [149]. It accounts for multilayer adsorption and non-uniform binding site energies and is expressed as:

$$q = K_F C^{1/n} \quad (2)$$

where q is the amount adsorbed, C is the equilibrium concentration, K_F is the Freundlich constant, and $1/n$ describes the adsorption intensity. This model is more suitable for real electrochemical interfaces such as polycrystalline gold electrodes, where surface heterogeneity and defect sites are present.

These models provide a theoretical framework for interpreting QCM and electrochemical data, where mass changes and charge transfer resistance variations reflect adsorption-driven interfacial processes.

From a broader perspective, similar adsorption patterns have been reported for other essential oil constituents such as linalool, citronellol, and limonene [150–152]. These studies generally confirm that hydrophobic EOs constituents tend to form surface-associated layers driven by weak intermolecular interactions and surface energy minimization. However, compared to smaller non-functional hydrocarbons, oxygen-containing monoterpenes such as geraniol show stronger and more structured adsorption due to the presence of polar functional groups.

Overall, adsorption plays a dual role in this system: it governs both analyte detection and polymer formation. In the present work, geraniol adsorption is not only a sensing-related phenomenon but also a key factor influencing the MIP architecture through its effect on monomer organization at the electrode interface. Therefore, adsorption studies provide essential mechanistic insight linking the surface chemistry, polymer formation, and sensor performance.

3.1.1. Cyclic voltammetry analysis of adsorption and polymerization processes

Cyclic voltammetry was used to evaluate interfacial processes during adsorption and electropolymerization on the Au electrode [153]. The recorded voltammograms provide direct insight into how template–surface interactions influence electron transfer and polymer growth [137,141,154].

In the absence of geraniol (1AD system), well-defined and stable voltammetric profiles were observed, indicating a reproducible electrochemical response of the supporting electrolyte and an unmodified electrode surface. The peak shapes and current intensities suggest that electron transfer processes occur without significant kinetic limitation. In contrast, the presence of geraniol (2AD system) resulted in a noticeable decrease in both anodic and cathodic peak currents. This reduction is consistent with partial

surface blocking, where adsorbed geraniol molecules reduce the effective electroactive area of the Au electrode (Figure 7). This phenomenon is commonly associated with adsorption-controlled processes, where surface coverage by organic molecules limits charge transfer between the electrode and electrolyte.

From a mechanistic viewpoint, this indicates that geraniol forms an interfacial layer prior to any polymerization process. This layer modifies the double-layer structure at the electrode interface, leading to a decreased electron transfer efficiency and an altered capacitive behavior. Similar effects have been reported for other hydrophobic analytes and EOs components, where adsorption leads to suppression of redox activity due to surface coverage effects.

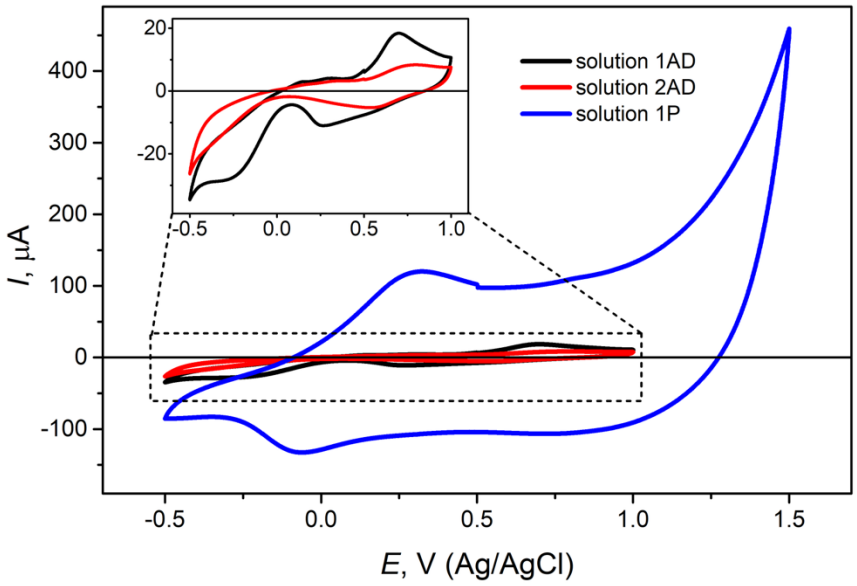

Figure 7. Comparison of CV responses for 1AD, 2AD, and 1P solutions. Measurements for 1AD and 2AD were performed in the potential range of −500 mV to +1000 mV vs. Ag/AgCl with three cycles at a scan rate of 100 mV/s. 1P system was measured separately under the same potential range with five cycles at 100 mV/s. The second cycle of each CV is shown [137]

During pyrrole polymerization (1P system), progressive increases in the current response were observed across successive cycles. This is a characteristic of conducting polymer growth, where continuous oxidation of pyrrole leads to the formation and thickening of a Ppy film. The increasing

current reflects an enhanced charge storage capacity and an increase in the electroactive surface area.

When geraniol is present (2P system), a significantly reduced increase in current is observed over the same potential range and number of cycles. This indicates that geraniol adsorption interferes with pyrrole oxidation and limits polymer propagation. As a result, nucleation sites for polymer growth are reduced, leading to a slower film formation and a lower overall polymer density.

This effect is particularly important in the context of molecular imprinting. Uniform polymer growth is essential for forming well-defined recognition cavities; however, adsorption of template molecules prior to and during electropolymerization can disturb monomer organization. This leads to heterogeneous film formation and variability in the binding site distribution, which directly affects the sensor performance.

The CV results therefore confirm that geraniol influences both adsorption and electropolymerization kinetics. The observed suppression of the current growth in the presence of geraniol demonstrates that template–electrode interactions extend beyond simple binding phenomena and actively modulate polymer formation pathways.

Overall, CV provides a powerful mechanistic tool for linking interfacial adsorption processes with polymer growth dynamics. In this system, CV not only confirms the presence of geraniol adsorption but also reveals its functional impact on pyrrole oxidation and Ppy formation, thereby directly connecting the surface chemistry with MIP structural evolution.

3.1.2. Electrochemical impedance spectroscopy analysis

Electrochemical impedance spectroscopy [155] was used to evaluate interfacial charge transfer processes and surface modifications induced by pyrrole and geraniol adsorption [156]. Adsorption directly modifies interfacial properties such as a double-layer structure, capacitance, and charge transfer resistance (R_{ct}) [157]. In particular, adsorbed species can block active sites and alter electron transfer kinetics, which is reflected in changes in R_{ct} and the constant phase element (*CPE*) [158].

In the context of MIP systems, EIS is widely used as a label-free transduction method because polymer formation and analyte binding events directly influence interfacial impedance. The formation of insulating or partially conductive polymer layers typically increases R_{ct}, whereas conductive polymer growth can decrease R_{ct} depending on the film morphology and the doping state. Similarly, adsorption of organic molecules

can either increase the capacitance (by increasing interfacial polarizability) or decrease it (by blocking access to the electrode surface), depending on the coverage and molecular orientation.

In this study, EIS was employed to evaluate interfacial charge transfer processes and surface modifications induced by pyrrole and geraniol adsorption in 1AD, 2AD, 1P, and 2P systems, both before and after cyclic voltammetry treatment (Figure 8).

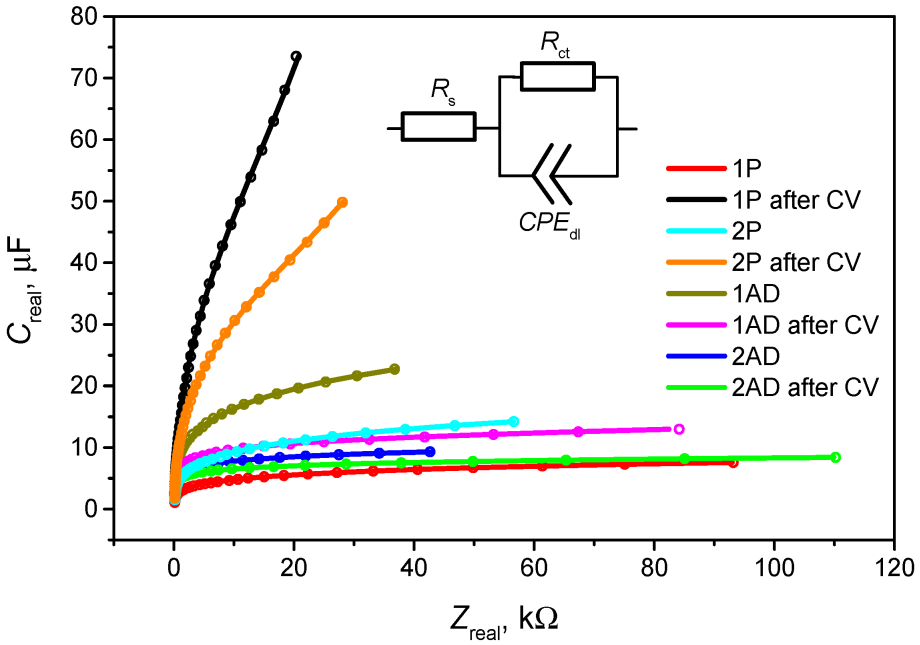

Figure 8. Comparison of EIS results for 1AD, 2AD, 1P, and 2P solutions before and after CV [137]

Measurements were performed over a frequency range of 10,000 Hz to 2 Hz. The impedance spectra were interpreted by using the Randles equivalent circuit, where R_s represents solution resistance, the *CPE* describes non-ideal double-layer capacitance, and R_{ct} reflects the resistance associated with interfacial charge transfer processes.

From the Nyquist representation, the diameter of the semicircle is directly associated with R_{ct}, while deviations from the ideal capacitive behavior reflect surface heterogeneity and adsorption-induced changes in the interfacial structure. A reduction in the semicircle diameter indicates enhanced charge transfer kinetics, whereas enlargement suggests surface blocking or the formation of an insulating layer.

The results demonstrate a clear distinction between pyrrole- and geraniol-containing systems. In the presence of pyrrole (1P system), a significant decrease in R_{ct} is observed, accompanied by an increase in capacitive response. This behavior confirms the formation of a conductive Ppy layer.

In contrast, geraniol-containing systems (2AD and 2P) show only minor changes in the impedance response. The relatively small variation in capacitance along with a limited change in R_{ct} suggest weak and non-conductive adsorption on the gold surface. This indicates that geraniol primarily acts as a surface-blocking species.

The observed increase in capacitance in pyrrole systems can be attributed to an enhanced interfacial polarizability and an increased effective surface area due to polymer growth. In contrast, geraniol adsorption leads to partial site occupation without significantly altering the electrochemical pathways, which is consistent with a physisorption-dominated mechanism.

Importantly, comparison before and after CV shows that the 1P system remains electrochemically active, thus indicating stable polymer formation and sustained interfacial modification. Geraniol-containing systems, however, do not show comparable evolution in the impedance parameters, thereby confirming limited participation in the electrochemical film growth processes.

Fitting of the impedance spectra when using the Randles equivalent circuit further supports these observations. Pyrrole significantly modifies both R_{ct} and *CPE* values, thus indicating strong interfacial restructuring due to polymer formation. Geraniol, in contrast, primarily affects the capacitive component without substantially contributing to conductive pathways. These results confirm that pyrrole governs electrochemical interface transformation through conductive polymer formation, while geraniol mainly influences surface accessibility through competitive adsorption. This distinction is critical for molecular imprinting, as it determines whether template molecules interfere with or merely coexist alongside polymer growth.

Overall, the EIS analysis demonstrates that interfacial impedance changes provide direct evidence of the adsorption strength, surface blocking behavior, and polymer formation dynamics. Together with CV and QCM, these results confirm that geraniol adsorption modulates MIP formation through interfacial competition with pyrrole.

3.1.3. Quartz crystal microbalance analysis and adsorption kinetics

Quartz crystal microbalance (QCM) was used to monitor adsorption processes in real time by measuring changes in the resonance frequency (Δf), which are proportional to mass changes at the sensor surface [159,160].

For rigid and thin films, the frequency shift is described by the Sauerbrey equation:

$$\Delta f = -\frac{2f_0^2}{A\sqrt{\rho_q \mu_q}}\Delta m \qquad (3)$$

where f_0 is the fundamental resonance frequency, A is the active electrode area, ρ_q is the density of quartz, and μ_q is the shear modulus of quartz. It enables conversion of frequency changes into the surface mass. In this study, the Sauerbrey approximation was considered valid due to low mass loading and a rigid adsorption mechanism.

The corresponding mass change can be calculated by rearranging the Sauerbrey relation:

$$\Delta m = -\frac{A\sqrt{\rho_q \mu_q}}{2f_0^2}\Delta f \qquad (4)$$

This provides direct evidence of mass accumulation at the interface. In more complex systems involving viscoelastic films or swelling polymers, alternative models such as the Voigt viscoelastic model are typically applied [161]. However, in the present study, the Sauerbrey approximation (Equations 3 and 4) was considered valid due to the low mass loading regime and the relatively rigid adsorption of the studied species.

QCM measurements in this work were used to investigate and compare the adsorption of pyrrole (a monomer) and geraniol (a template molecule) on gold-coated quartz surfaces. This approach provides direct experimental evidence of mass accumulation at the interface and complements electrochemical techniques, which primarily reflect electron transfer and capacitive changes. In the context of molecular imprinting, QCM is particularly valuable because it allows direct observation of template–monomer competition during the early stages of film formation.

During the experiments conducted in the framework of thus research, a technical limitation was encountered due to swelling of the 3D printed flow cell when exposed to pure acetonitrile. In order to maintain mechanical stability and ensure reproducible resonance signals, a 50:50 (v/v) acetonitrile–water mixture was used. This solvent composition preserved sufficient

solubility of geraniol while maintaining stable acoustic coupling conditions required for reliable QCM operation.

The adsorption experiments revealed distinct differences between pyrrole and geraniol. Pyrrole exhibited rapid and strong adsorption on the gold surface, resulting in a frequency shift of approximately −43 Hz at 0.5 M concentration. In contrast, geraniol at 0.05 M produced a smaller initial shift of approximately −10 Hz, thus indicating weaker but still measurable interaction with the surface.

Time-resolved measurements further demonstrated that geraniol adsorption is kinetically slower but persistent. Over a 30-minute interval, a gradual frequency decrease of approximately −38 Hz was observed, accompanied by a minor change in dissipation resistance (~4 Ω). This finding indicates progressive accumulation at the interface rather than instantaneous saturation, suggesting a diffusion-controlled adsorption regime combined with weak but stable surface affinity.

By using the Sauerbrey model (Eq. 4), the frequency shifts were converted into surface mass coverage. The calculated adsorption masses were approximately 7.6 ng/cm² for pyrrole and 1.77 ng/cm² for geraniol. Although pyrrole exhibits a higher absolute mass response, this is strongly influenced by its higher concentration and efficient surface adsorption kinetics.

To enable meaningful comparison between species with different concentrations, adsorption efficiency was normalized with respect to concentration. This normalization reveals that geraniol exhibits relatively high adsorption efficiency per concentration unit compared to pyrrole. This suggests that despite its lower bulk concentration, geraniol has a strong intrinsic affinity for the gold surface, consistent with its amphiphilic molecular structure.

To further interpret adsorption thermodynamics, the Langmuir adsorption model was applied, which assumes monolayer adsorption on a homogeneous surface with a finite number of identical binding sites. The model is expressed as follows:

$$q_{\mathrm{e}} = \frac{q_{\max} K C_{\mathrm{e}}}{1 + K C_{\mathrm{e}}} \qquad (5)$$

where q_{e} is the equilibrium adsorption capacity, $q_{\max}$ is the maximum adsorption capacity, K is the adsorption constant, and C_{e} is the equilibrium concentration.

The estimated adsorption constants (Eq. 5) were approximately 31.7 L/mol for pyrrole and 21.5 L/mol for geraniol. These values indicate strong surface affinity for both species, although pyrrole demonstrates higher

apparent adsorption strength due to its ability to participate in electropolymerization and form extended surface-bound networks.

However, because adsorption was evaluated at single concentration points for each analyte, full Langmuir or Freundlich isotherm fitting could not be performed. Therefore, the calculated constants should be interpreted as semi-quantitative indicators of surface affinity rather than full thermodynamic parameters.

From a mechanistic perspective, the results demonstrate clear competitive adsorption between pyrrole and geraniol on the gold surface. In mixed systems, geraniol partially occupies active adsorption sites, reducing the pyrrole surface availability and thereby influencing the nucleation density during electropolymerization. This leads to a slower Ppy growth and increased heterogeneity in the initial polymer layer formation.

These observations are fully consistent with electrochemical impedance spectroscopy results, which showed a reduced charge transfer efficiency and an altered interfacial capacitance in mixed systems. The agreement between QCM and electrochemical data confirms that adsorption is a governing factor in interfacial restructuring during molecular imprinting.

Overall, pyrrole acts as a strongly adsorbing and electroactive monomer which drives polymer formation, while geraniol exhibits weaker but persistent adsorption with significant competitive effects. Even at lower concentrations, geraniol effectively modifies surface accessibility and influences polymer growth pathways. These findings highlight the critical role of adsorption kinetics and surface competition in determining the structural and functional properties of molecularly imprinted polymer layers.

3.1.4. Implications for molecularly imprinted polymer formation

The adsorption observed for both geraniol and pyrrole have direct consequences for the formation, structure, and functional performance of MIP. Their formation at electrode interfaces is governed by three coupled processes: (i) template adsorption and pre-organization, (ii) monomer adsorption and complex formation, and (iii) electropolymerization-induced fixation of the supramolecular arrangement. Any imbalance in these steps can significantly alter the distribution, accessibility, and homogeneity of the resulting recognition cavities.

Geraniol exhibits strong and persistent adsorption on the gold surface, as demonstrated by QCM and electrochemical measurements. Although geraniol does not possess functional groups typically associated with strong chemisorption on gold surfaces, its adsorption is sufficiently stable to

influence interfacial electrochemical processes. The interaction is likely governed by weak physisorption mechanisms, including van der Waals interactions, hydrophobic effects, partial coordination of the hydroxyl group at the metal–solution interface, and interfacial molecular ordering effects. These interactions promote template pre-organization at the interface prior to polymer growth, thus increasing the likelihood of forming well-defined template–monomer assemblies required for selective recognition after template removal.

However, this strong surface affinity also introduces a limitation. Excessive adsorption of geraniol may lead to partial surface blocking, thus reducing the availability of active sites required for pyrrole adsorption and oxidation. This results in non-uniform monomer distribution and altered nucleation behavior, which can produce heterogeneous polymer thickness, irregular porosity, and uneven imprint site distribution.

Pyrrole, in contrast, is a well-established electroactive monomer which readily forms conductive Ppy films under electrochemical conditions. Its adsorption is strongly dependent on surface availability and is therefore highly sensitive to competition from pre-adsorbed species such as geraniol. When geraniol occupies a significant fraction of adsorption sites, pyrrole access to the electrode is reduced, leading to delayed nucleation and modified polymer growth kinetics.

Consequently, the formation of a high-quality MIP layer requires a carefully controlled balance between the template adsorption strength, monomer accessibility, and the polymerization rate. These parameters collectively define the organization of the pre-polymerization complex and determine the structural fidelity of the imprinted cavities.

From a broader perspective, the application of geraniol as a template in MIP systems is relatively limited compared to other analytes commonly used in imprinting studies. Most reported MIP systems target more structurally rigid molecules such as phenolic compounds, pharmaceutical agents (e.g., caffeine, dopamine, ibuprofen), and environmental pollutants (e.g., pesticides). These analytes typically possess well-defined functional groups and limited conformational flexibility, thus facilitating stable template–monomer interactions.

In contrast, geraniol presents several challenges. It is a flexible, acyclic monoterpene alcohol denoted by high hydrophobicity and conformational freedom, which can complicate the formation of stable and well-defined template–monomer complexes. Additionally, its relatively weak polarity and a limited number of interaction sites reduce the predictability of binding orientation during pre-polymerization.

Another important consideration is its activity in electrochemical environments. Geraniol is poorly soluble in water and often requires organic co-solvents such as acetonitrile or ethanol. As observed in this study, even under mixed-solvent conditions, interfacial accumulation can still occur, introducing diffusion limitations, local viscosity changes, and potential surface fouling. These effects may negatively affect the reproducibility of MIP formation.

Despite these challenges, structurally related terpenoid compounds such as linalool, citronellol, and limonene have been successfully incorporated into MIP-based sensing systems, particularly in applications involving volatile organic compound detection.

In this context, geraniol can be considered a representative yet challenging model compound for EOs analysis. Its successful integration into an MIP-based sensing platform demonstrates the feasibility of extending molecular imprinting strategies beyond rigid analytes to more flexible and hydrophobic molecules. However, this study also shows that careful control of interfacial adsorption and polymer growth is required to achieve reproducible performance**.**

Overall, the findings confirm that both the molecular properties of the template and its adsorption mechanism at the electrode interface are decisive factors in determining MIP performance. In the case of geraniol, strong surface affinity enables effective template localization but simultaneously introduces competitive effects that influence monomer organization and polymer morphology. These opposing effects must be balanced so that to achieve selective and reproducible sensor architectures.

3.2. Development and Electrochemical Characterization of MIP Layers

3.2.1. Design rationale and interfacial architecture

The design of MIP architectures in this study was guided by the adsorption of both pyrrole and geraniol, as established in the preceding sections [also, cf. 137]. In molecular imprinting systems, the performance of the final sensing layer is not only determined by the chemical composition of the polymer but is critically dependent on the organization of the pre-polymerization interface, where template–monomer–electrode interactions occur prior to and during film growth.

Molecular imprinting is fundamentally based on the formation of supramolecular assemblies between a functional monomer and a template molecule, followed by fixation of this arrangement through polymerization.

After the removal of the template, complementary cavities remain within the polymer matrix, exhibiting selective recognition properties toward the target analyte. In electrochemical MIP systems, this process is further influenced by the electrode surface, which acts not only as a physical support but also as an active participant in adsorption, nucleation, and electron transfer processes.

In the present system, a key challenge arises from the strong adsorption affinity of geraniol toward gold surfaces. As shown in previous sections, geraniol forms a persistent interfacial layer**,** which stabilizes the template but simultaneously competes with pyrrole for surface sites. This competition reduces monomer accessibility and affects nucleation behavior, leading to non-uniform polymer growth and a reduced control over the imprint site distribution.

To address this interfacial competition, a double-layer polymer architecture was implemented. This architecture consists of a NIP underlayer and a MIP top layer, each fulfilling distinct functional roles. The NIP layer is defined as a polymer film synthesized in the absence of template molecules, serving primarily as a structural and electrochemical interface modifier. Its main function is to improve adhesion of the polymer system to the gold electrode, stabilize the interfacial environment, and provide a more uniform surface for subsequent deposition.

Importantly, the NIP layer reduces the influence of substrate heterogeneity and partially regulates mass transport toward the interface, leading to more reproducible electropolymerization conditions.

The MIP layer is formed in the presence of geraniol and is responsible for the generation of selective recognition cavities. During electropolymerization, pyrrole is oxidized and forms a conjugated Ppy network around the adsorbed template molecules. After template removal, cavities complementary to geraniol in terms of the size, shape, and functional group distribution are retained within the polymer matrix.

The introduction of this bilayer configuration provides an important mechanistic advantage. It effectively separates two interdependent but potentially competing processes: interfacial stabilization and molecular imprinting. In conventional single-layer systems, these processes occur simultaneously at the electrode surface, which means that strong template adsorption can interfere directly with monomer organization and polymer growth. In contrast, the pre-formed NIP layer partially decouples the electrode surface from template–monomer competition, thereby enabling more controlled polymer growth in the upper layer.

This spatial separation leads to an improved regulation of interfacial phenomena. The NIP layer ensures stable and reproducible electrochemical

conditions, while the MIP layer preserves the molecular recognition functionality. As a result, the overall system benefits from an enhanced structural uniformity, an improved adhesion stability, and better-defined imprinting domains.

Such bilayer architectures can be interpreted as an interfacial engineering strategy, where control over surface properties is used to optimize both polymer growth and molecular recognition. Similar strategies have been reported in electrochemical MIP sensors where underlayers of conducting polymers or inert films are used to improve film stability and reproducibility, particularly in systems involving volatile or weakly polar templates. In this context, the NIP/MIP bilayer approach can be considered a form of interfacial engineering that optimizes both electrochemical performance and molecular recognition capability.

Overall, the proposed architecture demonstrates that successful MIP fabrication is not solely determined by chemical imprinting conditions but also by rational control of interfacial processes. In the case of geraniol, where adsorption is strong, and competitive effects are significant, the introduction of a structured underlayer is essential to ensure controlled monomer deposition and to maintain the integrity of the imprinting process. This design strategy therefore represents a key step toward improving reproducibility and functional performance in electrochemical MIP-based sensing systems.

3.2.2. Electropolymerization and film formation

The formation of Ppy films in this system was carried out by using CV, which enables simultaneous control of the oxidation state, polymer growth kinetics, and interfacial structure formation. Electropolymerization of pyrrole is an electrochemically driven process, in which, pyrrole monomers are oxidized at the electrode surface to form radical cation intermediates. These reactive species undergo rapid coupling reactions, leading to the formation of oligomers and eventually extended conjugated polymer chains. Continued potential cycling promotes further oxidation, chain propagation, and deposition of a conductive polymer film onto the electrode surface.

From a mechanistic perspective, Ppy film formation typically proceeds through three stages: (1) initial nucleation, (2) progressive growth, and (3) steady-state film thickening [162]. During the early cycles, adsorption of pyrrole and formation of radical cations dominate, resulting in localized nucleation sites on the electrode. As cycling continues, these nuclei grow into interconnected polymer domains, gradually forming a continuous conductive

network. The final stage is characterized by diffusion limitations and partial passivation of the electrode surface due to the increasing film thickness.

In this work, CV was also used as a tool to indirectly monitor interfacial evolution during polymer growth. Changes in the peak current, peak shape, and the overall current density were used as indicators of electron transfer kinetics and the active surface area, thus allowing an indirect evaluation of the film formation.

To evaluate the influence of interfacial architecture on film formation, three distinct configurations were designed. These configurations were not only intended for comparative analysis but also to decouple the contributions of the template presence, surface conditioning, and polymer growth dynamics (Figure 9).

The first configuration corresponds to a single-layer MIP system, in which, pyrrole and geraniol were simultaneously present during electropolymerization. In this case, polymer formation and molecular imprinting occur concurrently at the same interface. While this approach enables direct incorporation of the template into the growing polymer matrix, it also exposes the electrode surface to strong competitive adsorption effects. However, as discussed previously, and as it has been demonstrated, geraniol can occupy active surface sites and interfere with pyrrole adsorption, thereby influencing the nucleation density and leading to spatially non-uniform polymer growth. This results in imprint sites that are formed under dynamically changing interfacial conditions, which may reduce the structural uniformity of the final recognition cavities (Figure 9A).

The second configuration is a double-layer MIP system, which introduces a sequentially constructed architecture. In this case, a NIP base layer is first deposited in the absence of geraniol under identical electrochemical conditions. This initial layer serves as an interfacial conditioning and stabilization platform. After the formation of the NIP layer, a second electropolymerization step is performed in the presence of geraniol, enabling the imprinting to occur on a pre-stabilized surface (Figure 9B).

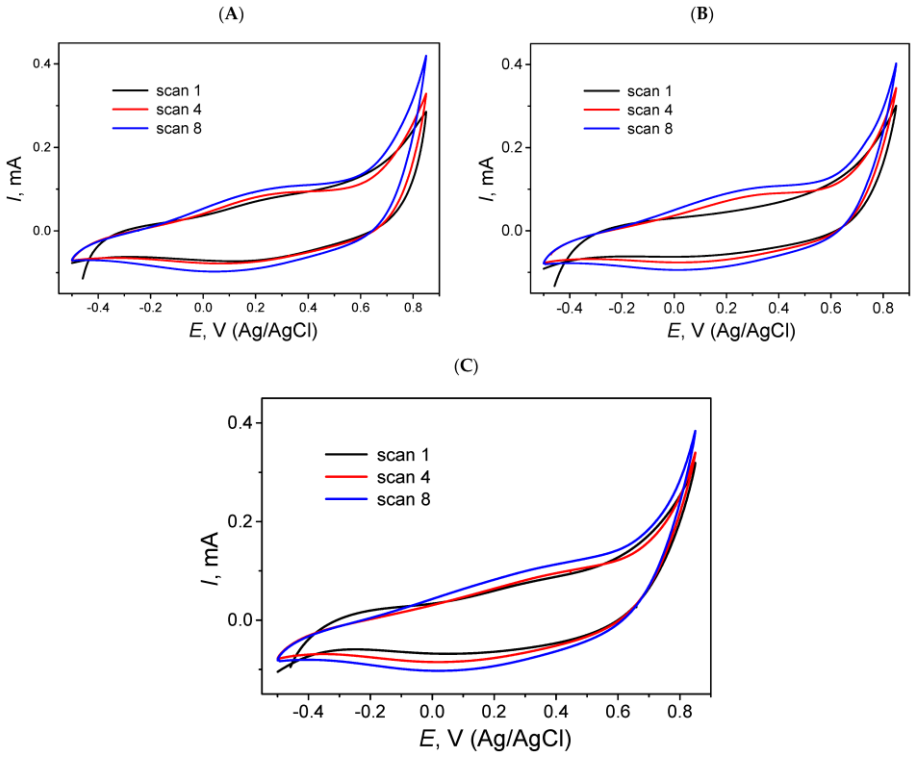

Figure 9. Electropolymerization of polypyrrole films on the QCM (Au) sensor was carried out under controlled cyclic voltammetry conditions. (A) Single-layer MIP was formed over 8 CV cycles within −500 to +850 mV at 50 mV s^{-1}. (B) Double-layer MIP was prepared by using the same conditions with an initial 7-cycle base layer followed by additional deposition. (C) NIP was synthesized under identical parameters for 7 cycles to ensure comparable film formation [132]

From an electrochemical standpoint, the presence of the NIP underlayer significantly modifies interfacial properties. It reduces heterogeneity associated with the gold substrate, provides a more uniform energy landscape for monomer adsorption, and stabilizes electron transfer processes during polymer growth. This leads to a more reproducible nucleation behavior and improved control over film thickness and morphology. In addition, the NIP layer partially decouples the electrode from the direct template–surface competition, thereby reducing the disruptive influence of geraniol adsorption during polymerization.

The third configuration corresponds to a NIP reference system, prepared under identical conditions but in the absence of the template molecule (Figure 9C). This system provides a baseline for evaluating the

intrinsic electrochemical and morphological properties of Ppy films without imprinting effects. It allows discrimination between changes arising from molecular recognition and those originating from the general polymer growth process.

Across all configurations, the electrochemical response during polymerization confirmed successful formation of conductive Ppy films, as evidenced by the progressive increase in the oxidation peak currents and stabilization of redox features over successive cycles. However, important differences were observed in the growth mechanism depending on the interfacial architecture.

The single-layer MIP system exhibited more variable current evolution, which was consistent with heterogeneous nucleation and dynamic competition between pyrrole and geraniol at the electrode surface. In contrast, the double-layer configuration showed more stable and reproducible current patterns, thus indicating more controlled polymer growth. This observation suggests that the NIP underlayer promotes uniform monomer organization and reduces fluctuations in local interfacial conditions during electropolymerization.

From a materials perspective, these differences are highly significant for molecular imprinting. Uniform polymer growth is directly linked to consistent distribution of recognition cavities, while heterogeneous growth can lead to variability in the binding site accessibility and affinity. Thus, the improved stability observed in the double-layer system directly supports an enhanced imprint quality.

Overall, these results demonstrate that electropolymerization in MIP systems is not solely a chemical polymerization process, but a highly interface-sensitive phenomenon governed by adsorption dynamics, surface heterogeneity, and interfacial architecture. The introduction of a NIP base layer provides a controlled platform for the subsequent imprinting, enabling a more predictable film growth and an improved structural definition of the resulting recognition layer.

3.2.3. Interfacial behavior and QCM analysis

The interfacial adsorption of geraniol on the fabricated sensing architectures was investigated when using QCM, which enables real-time, *in-situ* monitoring of mass changes at the electrode interface. In QCM measurements, variations in Δf arise from changes in the effective mass coupled to the oscillating quartz crystal. This allows direct observation of adsorption, desorption, and film restructuring processes occurring at the solid–liquid

interface. In addition to frequency shifts, dissipation-related parameters provide insight into the viscoelastic properties of the interfacial layer (Figure 10).

From a mechanistic perspective, QCM not only reflects the adsorption strength but also provides insight into the structural organization and mechanical stability of the interfacial layers. In rigid systems, frequency shifts can be interpreted quantitatively by using the Sauerbrey relation (Equations 3 and 4), whereas deviations from the ideal behavior indicate viscoelastic contributions, structural heterogeneity, or partial mass trapping within porous polymer networks.

The results obtained in this study demonstrate that geraniol adsorption is strongly dependent on the architecture of the polymer layer. In the single-layer MIP configuration, adsorption is characterized by unstable frequency recovery and incomplete desorption. This indicates partial retention of geraniol within the polymer matrix, suggesting the presence of heterogeneous binding environments with varying accessibility and affinity.

This irreversible or partially reversible adsorption can be attributed to non-uniform polymer growth during simultaneous template–monomer electropolymerization. As previously shown, direct competition between geraniol and pyrrole at the electrode surface leads to spatially uneven nucleation and growth of Ppy. Consequently, the resulting polymer film contains regions with different porosity, crosslinking density, and diffusion accessibility. These structural irregularities create deep or partially occluded binding sites where geraniol molecules can become kinetically trapped, leading to incomplete desorption and baseline drift in the QCM signal (Figure 10A).

In contrast, the double-layer MIP system exhibits a significantly improved interfacial behavior. In this configuration, the frequency response stabilizes more rapidly after analyte exposure and shows a higher degree of reversibility during the desorption phase (Figure 10B). Reduced hysteresis between adsorption and desorption cycles indicates a more uniform binding site accessibility and an improved mass transport within the polymer layer.

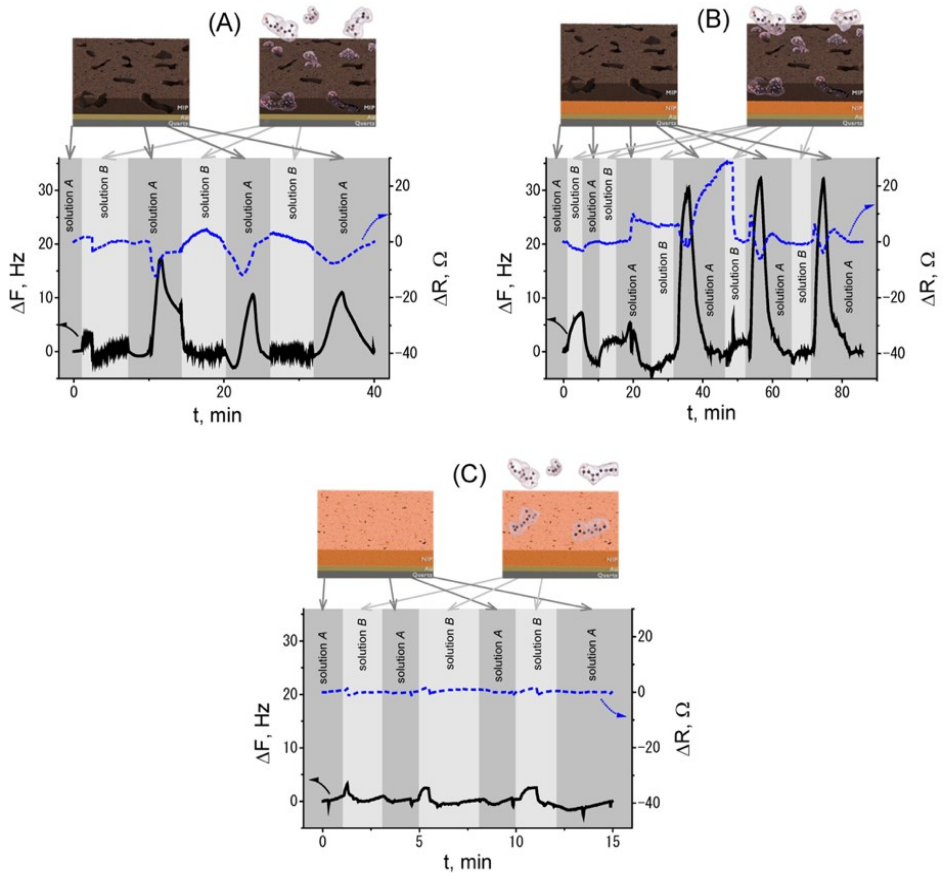

Figure 10. QCM response of different polymer layers toward Solution B. The solid black line represents the change in the *Δf* value of the QCM sensor, while the dotted blue curve represents the change in the resistive element ΔR of the QCM sensor. (A) QCM measurement of the single-layer MIP at a flow rate of 1 mL min^{-1}. The rectangle highlights the response to Solution B. (B) QCM measurement of the double-layer MIP at a flow rate of 1 mL min^{-1}. The rectangle indicates the response to Solution B at 100% concentration exposure. (C) QCM measurement of the NIP on the QCM (Au) sensor at a flow rate of 1 mL min^{-1}. The rectangle marks the response to Solution B at 100% concentration exposure [163]

This improvement can be attributed to the presence of the NIP underlayer, which modifies the interfacial energy landscape and provides a structurally homogeneous foundation for subsequent imprinting. By reducing direct interaction between the gold substrate and the imprinting process, the NIP layer minimizes surface-induced heterogeneity during polymer growth.

This leads to more controlled nucleation, an improved film continuity, and reduced formation of structurally weak or over-constrained binding domains.

From a materials and interfacial mechanics perspective, the differences between single-layer and double-layer systems can be explained in terms of the polymer morphology and diffusion accessibility. In the single-layer system, direct growth on the gold surface results in strong sensitivity to local variations in the surface energy, which promotes heterogeneous film formation. These irregularities increase diffusion barriers for analyte removal and enhance the probability of analyte entrapment within deeper polymer regions.

In contrast, the double-layer architecture promotes a more defined and reproducible interfacial structure. The NIP layer acts as a mechanical and chemical buffer, reducing interfacial disorder and supporting more uniform distribution of imprinted sites in the upper layer. As a result, the MIP layer exhibits an improved accessibility of binding cavities, a more efficient mass transport, and reduced kinetic hindrance during adsorption–desorption cycles. These structural improvements are directly reflected in the increased stability of the QCM frequency baseline and reduced signal hysteresis.

Additional QCM analysis further confirms that geraniol adsorption is not fully reversible under all conditions. A residual frequency shift remains after repeated adsorption–desorption cycles, indicating partial retention of analyte molecules within the polymer structure. This behavior is attributed to a combination of diffusion limitations and heterogeneous binding sites rather than a single adsorption mechanism.

Such effects are particularly relevant in molecular imprinting systems, as incomplete analyte removal can reduce the number of available binding sites in the subsequent cycles and affect sensor regeneration performance. Therefore, the observed residual mass signal is not only an experimental artifact but also an important indicator of internal diffusion limitations and structural heterogeneity within the polymer matrix.

Overall, QCM results provide strong evidence that polymer architecture plays a decisive role in controlling adsorption reversibility, mass transport, and interfacial stability. The double-layer configuration offers a more controlled and reversible adsorption environment, thus confirming its superiority for reliable molecular recognition in geraniol-based MIP systems.

3.2.4. Quantitative interpretation of mass and molecular uptake

To obtain quantitative understanding of interfacial adsorption, the experimentally measured frequency shifts obtained by QCM were converted

into surface mass changes. This conversion is based on the Sauerbrey model (3-4), which describes the linear relationship between frequency decrease and rigid mass loading on the surface of a piezoelectric quartz crystal. The fundamental assumption of this model is that the adsorbed layer behaves as a rigid, thin, and uniformly distributed film that is fully coupled to the oscillation of the crystal.

Under these conditions, the relationship between the frequency change and the mass change is linear and can be simplified by using a calibration constant (C), which is experimentally determined for a given crystal frequency:

$$\Delta m = C \cdot \Delta f \qquad (6)$$

In this study, a Sauerbrey constant of C = 17.7 ng·Hz^{-1} (5 MHz crystal) was used, allowing direct conversion of frequency shifts into mass changes (6). While deviations from the ideal Sauerbrey behavior may occur in viscoelastic polymer systems, the relatively low mass loading observed here supports the validity of the rigid-layer approximation.

The experimentally derived frequency shifts were converted into absolute mass changes, which were subsequently normalized by the electrode area in order to obtain surface coverage (Γ):

$$\Gamma = \frac{\Delta m}{A} \qquad (7)$$

where A represents the active electrode area. This parameter provides a direct measure of the extent of the density at which the analyte molecules occupy the interfacial region.

To further extend the analysis, the mass values were converted into molar quantities by using the molecular weight of geraniol and then to the number of molecules calculated.

This step enables transformation of macroscopic QCM signals into molecular-scale interpretation, allowing estimation of the interfacial population density and comparative adsorption efficiency between different polymer architectures.

The quantitative results reveal a clear distinction between single-layer and double-layer MIP systems (Table 3). The double-layer configuration exhibits a significantly larger frequency shift (−34 Hz), corresponding to a calculated mass increase of approximately 6.02×10^{-7} g (≈ 602 ng). In contrast, the single-layer system shows a substantially lower response (~1.36 Hz), corresponding to approximately 24 ng of adsorbed mass. This indicates a substantially higher adsorption capacity in the double-layer architecture.

When normalized to the electrode area, the double-layer system reaches a surface coverage on the order of 3.0×10^{-6} g·cm^{-2}, which is approximately two orders of magnitude higher than that observed in the single-layer configuration. This suggests that the interfacial architecture plays a dominant role in determining effective molecular accumulation at the sensing interface.

At the molecular level, the calculated adsorption corresponds to approximately 3.90×10^{-9} mol of geraniol in the double-layer system, which translates into approximately 2.35×10^{15} molecules. When expressed as surface density, this yields values on the order of 10^{16} molecules·cm^{-2}. Such values exceed those expected for ideal monolayer coverage and therefore indicate effective mass loading which includes both surface adsorption and partial incorporation of molecules within the polymer matrix.

Table 3. Quantitative analysis of geraniol adsorption on MIP-modified QCM electrodes [132]

Parameter	Formula / Symbol	Single-layer MIP (0.05 mol·L^{-1})	Double-layer MIP (0.05 mol·L^{-1})
Frequency shift	Δf	~1.36 Hz	−34 Hz
Measured mass change	Δm	2.407×10^{-8} g (24 ng)	6.02×10^{-7} g (~602 ng)
Surface coverage	$\Gamma = \Delta m / A$	1.20×10^{-7} g·cm^{-2} (120.35 ng·cm^{-2})	3.0×10^{-6} g·cm^{-2} (~3000 ng·cm^{-2})
Moles adsorbed	$n = \Delta m / MW$	1.56×10^{-10} mol	3.90×10^{-9} mol
Total molecules adsorbed	$N = n \times N_A$	9.40×10^{13} molecules	2.35×10^{15} molecules
Molecules per unit area	N / A	4.70×10^{14} molecules·cm^{-2}	1.18×10^{16} molecules·cm^{-2}

Constants in use: $C = 17.7$ ng·Hz^{-1} (Sauerbrey constant, 5 MHz crystal); $A = 0.20$ cm^2 (active electrode area); $MW = 154.25$ g·mol^{-1} (geraniol); $N_A = 6.022 \times 10^{23}$ mol^{-1}

It is of importance to note that such high molecular densities should be interpreted as effective surface loading rather than discrete monolayer formation, since QCM measurements may include contributions from both directly adsorbed molecules and partially infiltrated species within the polymer matrix. This is particularly relevant in porous or heterogeneous MIP structures, where diffusion into subsurface cavities may contribute to the total frequency response.

From a mechanistic perspective, these quantitative findings confirm that the double-layer architecture significantly enhances both the adsorption capacity and the molecular retention at the interface. This improvement arises

primarily from an improved structural organization and the accessibility of binding sites, rather than simply an increased surface area.

Overall, the QCM-based quantitative analysis provides direct molecular-level evidence that interfacial engineering strongly influences the adsorption capacity, molecular packing density, and effective recognition site accessibility in MIP systems.

3.2.5. Kinetic modelling of adsorption and desorption processes

To understand the dynamic interaction of geraniol with the polymer-modified electrode surface, adsorption and desorption processes were analyzed by using a kinetic framework based on surface reaction theory. Such modelling is widely used in studies involving MIP and QCM systems, where the measured frequency shift reflects real-time changes in interfacial mass loading. In these systems, kinetic analysis provides not only rate constants but also mechanistic insight into how molecules interact with heterogeneous polymer interfaces. From a physicochemical perspective, adsorption at solid–liquid interfaces are governed by a combination of diffusion, surface collision, and binding processes. In the case of geraniol, the adsorption process involves transport from the bulk solution toward the polymer surface, followed by interaction with available binding sites distributed within the Ppy matrix. These sites include both non-specific adsorption regions and specific cavities generated during the imprinting process (Figure 11).

The interaction between geraniol and the polymer surface can be described as a reversible binding process, where geraniol molecules associate with and dissociate from active surface sites. These sites are not chemically uniform but, instead, represent a distribution of energetically different environments within the polymer structure.

In MIP systems, this behavior is often approximated by using a Langmuir-type adsorption framework, which assumes: a finite number of binding sites, monolayer coverage at the interface, and no strong lateral interactions between adsorbed molecules [164].

Although real MIP systems deviate from the idealist one due to surface roughness, heterogeneous porosity, and uneven crosslinking density, the Langmuir model remains widely used because it provides a useful first-order approximation for interpreting QCM-derived kinetic data.

In the present system, adsorption is governed by interactions between geraniol molecules in the solution and active binding sites within the polymer matrix. These interactions arise from a combination of weak intermolecular forces, including van der Waals interactions, hydrophobic effects, and

hydrogen bonding associated with the hydroxyl functional group of geraniol [165]. As a result, the overall binding process is stronger than simple physisorption, and yet it remains reversible under dynamic flow conditions typically applied in QCM-based measurements.

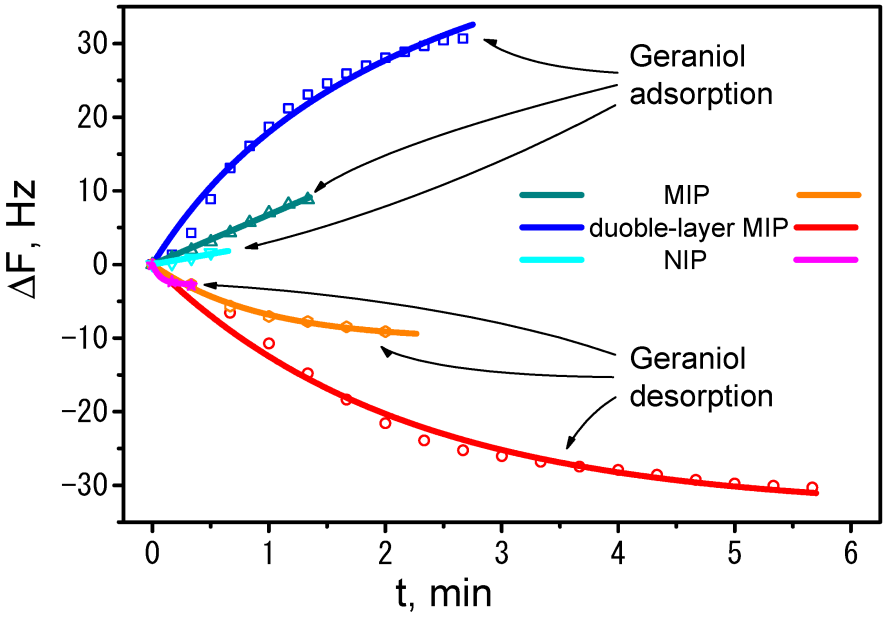

Figure 11. Adsorption and desorption kinetic data for geraniol, derived from the Δf curves, are presented as experimental data points. The corresponding theoretical Δf profiles are displayed as solid lines [132]

From a mechanistic standpoint, adsorption proceeds through a sequence of steps beginning with the diffusion of geraniol molecules from the bulk solution toward the polymer interface. Upon reaching the surface, the molecules transiently interact with the available binding sites and may either form a stable surface complex or return to the solution phase. At a low surface coverage, the adsorption rate is relatively high due to the abundance of unoccupied binding sites. As adsorption progresses, the number of available sites decreases, leading to a gradual reduction in the adsorption rate until an equilibrium has been reached. This is a characteristic of saturation-controlled surface kinetics and is commonly described within the framework of Langmuir-type adsorption processes.

In QCM experiments, adsorption is directly reflected as a decrease in the resonance frequency, corresponding to an increase in the interfacial mass. Consequently, the time-dependent evolution of the frequency signal can be

interpreted as a direct representation of the surface coverage development. This relationship enables not only qualitative observation of adsorption but also quantitative analysis of the adsorption kinetics and equilibrium states.

The kinetic parameters obtained from the adsorption–desorption analysis provide valuable insights into the interfacial response of geraniol on different polymer architectures (Table 4). The adsorption rate constant k_{ads} reflects the efficiency of mass transport and binding of geraniol molecules at the polymer surface, incorporating both diffusion from the bulk solution and interaction with the available binding sites. The desorption rate constant k_{des} characterizes the stability of the formed surface complexes and their tendency to dissociate over time. The equilibrium association constant K_{asoc}, defined as the ratio of k_{ads} to k_{des}, represents the overall affinity of geraniol toward the polymer interface.

As summarized in Table 4, significant differences are observed between the studied systems. The double-layer MIP exhibits a substantially higher adsorption rate constant k_{ads}= 0.420 compared to both the single-layer MIP (7.58×10^{-4}) and the NIP (3.35×10^{-4}), thus indicating a markedly more efficient uptake of geraniol at the interface. This enhanced adsorption behavior suggests an improved accessibility and a higher density of effective binding sites in the double-layer architecture. At the same time, the desorption rate constant for the double-layer system k_{des} = 0.469 remains moderate, which indicates that the formed complexes are sufficiently stable while still allowing partial reversibility.

In contrast, the single-layer MIP demonstrates a much lower adsorption rate combined with a relatively high desorption tendency, resulting in a significantly lower equilibrium constant K_{asoc} = 6.95 x 10^{-4}. This behavior suggests less efficient formation of stable binding interactions, which can be attributed to structural heterogeneity and limited accessibility of imprinted cavities when the polymer is formed directly on the electrode surface. The NIP system further highlights the importance of imprinting, as it exhibits both low adsorption efficiency and a very high desorption rate k_{des} = 14.5, leading to a negligible affinity constant K_{asoc} = 2.31 x 10^{-5}. This confirms that, in the absence of specific recognition sites, geraniol interacts only weakly and non-selectively with the polymer matrix.

Table 4. Kinetic parameters of geraniol adsorption [132]

	k_{ads}	k_{des}	K_{asoc}
MIP	$7.58 \times 10^{-4} \pm 0.019$	1.09 ± 0.028	6.95×10^{-4}
double-layer MIP	0.420 ± 0.0215	0.469 ± 0.008	0.895
NIP	$3.35 \times 10^{-4} \pm 0.216$	14.5 ± 0.835	2.31×10^{-5}

The desorption process follows first-order kinetics, as it depends on the concentration of the adsorbed species rather than on the bulk analyte concentration. In QCM measurements, this is reflected as a gradual recovery of frequency toward the baseline values. However, complete reversibility is not observed, thus indicating partial retention of geraniol within the polymer matrix.

This incomplete desorption arises from heterogeneous binding environments and diffusion limitations within the polymer structure, where molecules may be trapped in high-affinity cavities or less accessible regions.

Overall, the kinetic mechanism reflects a heterogeneous interface, where a fraction of molecules is weakly bound and readily desorbs, while another fraction exhibits stronger and slower-release interactions. Thus, the system is better described as an apparent Langmuir-type process rather than an ideal homogeneous model.

From a practical perspective, adsorption kinetics determine the sensor response time, while desorption properties influence regeneration and signal stability. The observed balance between the relatively fast adsorption and partial reversibility indicates that the double-layer MIP provides a strong analytical response while maintaining the potential for repeated use.

3.2.6. Electrochemical impedance spectroscopy and interfacial charge behavior

EIS was employed to investigate the electrical properties of the polymer-modified interfaces and to obtain mechanistic insights into charge transfer and adsorption phenomena occurring at the electrode surface. EIS is particularly suitable for such analysis because it enables the deconvolution of complex interfacial processes by applying a small-amplitude alternating potential over a broad frequency range, thereby separating resistive and capacitive contributions associated with different physicochemical processes.

All measurements were carried out in a classical three-electrode configuration integrated within the QCM cell. An Au electrode served as the working electrode and sensing interface, and an Ag/AgCl electrode functioned as the reference electrode, while a platinum wire was used as the counter-

electrode. This configuration ensures stable potential control and reliable separation of faradaic and non-faradaic processes, which is essential for accurate impedance analysis of surface-modified systems.

The Au working electrode was modified with different Ppy-based architectures, including single-layer MIP, double-layer MIP (NIP underlayer + MIP top layer), and NIP. The resulting impedance spectra, presented as Nyquist plots, are shown in Figure 12, where experimental data points are accompanied with fitted curves obtained by using an appropriate equivalent circuit model.

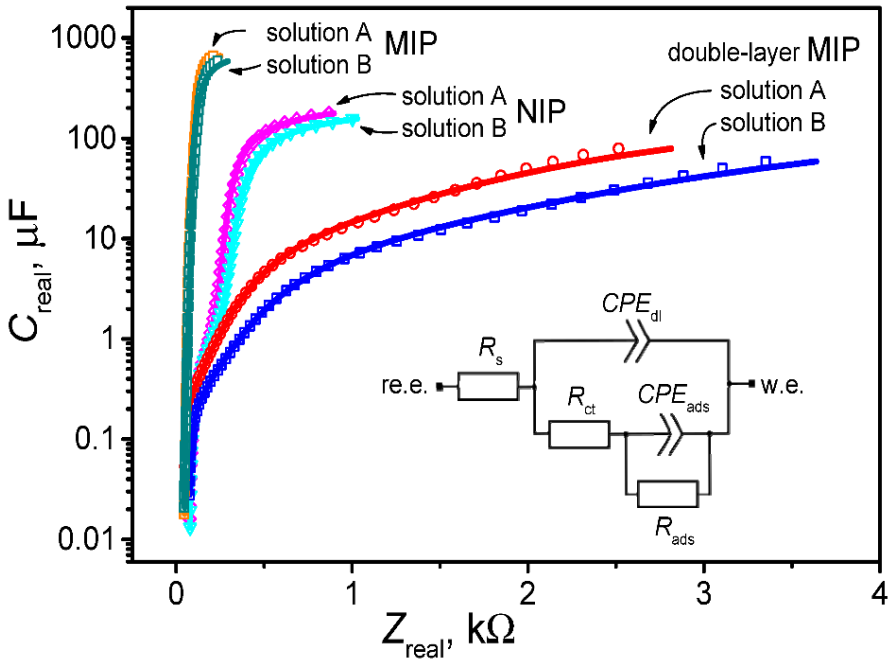

Figure 12. EIS were recorded by using the gold working electrode of a QCM sensor modified with different Ppy layers, including MIP, double-layer MIP, and NIP configurations. Measurements were carried out in both solution A and solution B. The experimental data are presented as discrete points, while the solid lines correspond to the fitted curves obtained by using the proposed equivalent circuit model [132]

To quantitatively interpret the impedance response, a modified Randles equivalent circuit was applied. In this model, the symbol R_s accounts for the ohmic resistance of the electrolyte, which remained nearly constant across all experiments due to the identical solution composition. The interfacial region is described by a CPE_{dl}, representing the non-ideal capacitive behavior of the

electrical double layer arising from surface roughness, heterogeneity, and polymer morphology. R_{ct} reflects the kinetics of electron transfer across the electrode–electrolyte interface and is highly sensitive to the surface coverage and film conductivity.

In addition to these classical elements, adsorption-related processes were incorporated into the model through a second constant phase element (CPE_{ads}) and an associated adsorption resistance (R_{ads}). These elements account for changes in the interfacial properties caused by analyte binding and structural reorganization within the polymer layer. Notably, R_{ads} values exceeded 1 GΩ in all cases, thereby indicating that adsorption does not significantly contribute to resistive impedance under the applied conditions, but rather manifests primarily through capacitive effects.

The extracted fitting parameters are summarized in Table 5. The analysis reveals that exposure to a geraniol-containing solution (Solution B) leads to a consistent decrease in the double-layer capacitance across all investigated systems, as reflected by reduced CPE_{dl} values. This decrease can be attributed to the displacement of electrolyte ions and solvent molecules from the interface, as well as to the incorporation of geraniol into the polymer structure, which alters both the dielectric properties and the effective thickness of the interfacial region.

Table 5. Equivalent parameters obtained from a digital fitting procedure applied to EIS data [132]

	Solution	CPE_{dl}, μS·s$^{\alpha}$	α_{dl}	CPE_{ads}, μS·s$^{\alpha}$	α_{ads}	R_{ct}, Ω
MIP	A	389 ± 203	0.625 ± 0.067	559 ± 147	0.862 ± 0.045	59.7 ± 12.7
	B	272 ± 155	0.598 ± 0.069	596 ± 119	0.812 ± 0.035	54.1 ± 9.55
double-layer MIP	A	2.30 ± 1.39	0.841 ± 0.057	188 ± 11.5	0.445 ± 0.015	144 ± 37.7
	B	0.91 ± 0.78	0.915 ± 0.079	153 ± 9.32	0.424 ± 0.016	129 ± 57.7
NIP	A	34.7 ± 7.96	0.639 ± 0.027	225 ± 13.0	0.792 ± 0.017	220 ± 12.1
	B	23.9 ± 4.64	0.677 ± 0.023	207 ± 10.7	0.783 ± 0.017	261 ± 12.4

Importantly, the magnitude of this effect strongly depends on the polymer architecture. The most pronounced change was observed for the double-layer MIP system, where the double-layer capacitance decreased by approximately 2.5-fold upon exposure to geraniol. In contrast, the single-layer MIP and NIP systems exhibited significantly smaller changes, with reduction factors of approximately 1.4. This indicates that the double-layer architecture undergoes a more substantial interfacial reorganization in response to analyte binding.

From a mechanistic standpoint, this behavior suggests that the double-layer MIP provides a more accessible and structurally defined binding environment. The NIP underlayer acts as a stabilizing platform which reduces direct interactions between geraniol and the gold surface, thereby promoting more uniform polymer growth and facilitating the formation of well-defined recognition cavities in the overlying MIP layer. As a result, geraniol binding induces more pronounced changes in interfacial polarization and charge distribution, which are directly captured by the impedance response.

In contrast, the NIP system exhibits predominantly non-specific adsorption, leading to only minor perturbations in the interfacial structure and electrical properties. Similarly, the single-layer MIP shows an intermediate response, where partial imprinting occurs but is limited by structural heterogeneity and less controlled film formation.

Changes in charge transfer resistance further support these observations. Systems with more uniform and conductive polymer films tend to exhibit lower R_{ct} values, while increased surface blocking or disordered structures lead to higher resistance. The relatively stable or moderately reduced R_{ct} values observed for the double-layer MIP indicate that, despite analyte binding, the conductive network of the polymer remains intact, which is essential for maintaining sensor functionality.

Overall, the EIS results demonstrate that the double-layer MIP architecture provides the most favorable balance between selective analyte recognition and stable electrochemical performance. The observed impedance changes are therefore not merely a consequence of non-specific adsorption but rather reflect specific interactions between geraniol and imprinted binding sites, thereby confirming the effectiveness of the designed sensing interface.

3.2.7. Regeneration behavior and stability considerations

Regeneration experiments revealed that the QCM frequency signal does not fully return to its initial baseline following desorption, which indicates partial

irreversibility of geraniol binding within the polymer matrix. This mechanism was observed for both single-layer and double-layer MIP systems; however, the double-layer configuration demonstrated an improved signal stability and a reduced baseline drift over repeated adsorption–desorption cycles. This improvement can be attributed to the presence of the NIP underlayer, which acts as a mechanically and structurally stabilizing interface. By partially decoupling the imprinted layer from the gold substrate, this intermediate layer reduces interfacial stress, limits structural rearrangement, and helps preserve the integrity of the polymer network during repeated operation.

From a mechanistic perspective, incomplete regeneration can be explained by several concurrent phenomena. First, a fraction of geraniol molecules is likely bound within high-affinity imprinted cavities, where multiple interactions (hydrophobic interactions combined with hydrogen bonding) stabilize the analyte–polymer complex. Second, diffusion limitations within the polymer matrix may hinder complete desorption, particularly for those molecules that penetrate deeper into the porous structure. Third, structural heterogeneity of the polymer layer results in a distribution of binding site energies, leading to a combination of reversible and quasi-irreversible adsorption domains. These effects are characteristic of molecularly imprinted systems and are commonly associated with non-ideal, heterogeneous binding activity.

Although the double-layer architecture improves reversibility, incomplete regeneration remains a limitation for practical sensor applications. In analytical systems, this manifests as a signal drift, reduced reproducibility, and gradual loss of active binding sites. To address these challenges, further optimization strategies should be considered. These include the modification of washing protocols using stronger eluents, mixed solvent systems, or pH-adjusted solutions; reduction of the polymer thickness to enhance mass transport; and tuning of the polymer structure toward lower crosslinking density or an increased flexibility to facilitate the analyte release.

It is also important to note that the present study was conducted at relatively high geraniol concentrations (0.025–0.05 $mol \cdot L^{-1}$) under controlled conditions and in the absence of structurally similar interfering compounds. While these conditions are suitable for fundamental mechanistic investigation, they do not fully represent real-life analytical environments, and, particularly, complex matrices such as essential oils. In such systems, multiple terpenoid compounds with similar structures – such as nerol, linalool, or citronellol – may compete for the binding sites, thus potentially affecting both selectivity

and regeneration. Therefore, the current conclusions regarding sensor performance should be considered as preliminary findings.

Future studies should focus on evaluating sensor performance under more realistic conditions, including lower analyte concentrations, competitive binding scenarios, and complex sample matrices. Key performance parameters such as the limit of detection, selectivity coefficients, regeneration efficiency, and long-term operational stability should be systematically assessed in order to determine practical applicability.

From a broader perspective, the observed strong retention of geraniol within the MIP structure highlights not only limitations but also opportunities. The ability of the polymer to retain target molecules suggests potential applications beyond sensing, including selective extraction, preconcentration, or controlled release systems. However, successful implementation of such applications will require precise control over the binding strength and reversibility, as well as a deeper understanding of the mass transport processes within the polymer network.

Overall, the combined EIS and QCM results demonstrate that the polymer architecture plays a decisive role in governing interfacial adsorption, electrical response, and regeneration. The double-layer MIP system represents a significant improvement in terms of the structural stability and signal reproducibility; however, further optimization is required to achieve fully reversible binding and a robust long-term performance. These findings provide a critical foundation for the rational design of next-generation MIP-based electrochemical sensors with an enhanced stability, selectivity, and practical applicability.

3.3. Surface Morphology and Layer Characterization by Using AFM

3.3.1. Role of AFM in characterization of MIP systems

The surface morphology of the fabricated Ppy layers was investigated by using AFM to evaluate the structural characteristics of the imprinted polymer interfaces at the nanoscale. AFM is a powerful surface characterization technique that provides high-resolution three-dimensional topographical mapping and enables quantitative analysis of parameters such as the surface roughness, height distribution, grain size, and spatial heterogeneity [166]. Here, quantitative assessment of structural heterogeneity refers to the statistical evaluation of nanoscale variations in the surface morphology and organization, including local differences in roughness, feature dimensions,

grain distribution, and spatial arrangement across the sample surface. However, in many applications, the main limitation arises not from the AFM technique itself but from the sample preparation, as obtaining an atomically flat substrate suitable for reliable nanoscale topographical analysis can be challenging. In the context of MIP, these parameters are of particular importance, as the formation of recognition sites is intrinsically related to the local organization of the polymer matrix generated during template-assisted polymerization.

From a mechanistic standpoint, the morphology of MIP layers is governed by several interdependent factors, including monomer adsorption, nucleation density during electropolymerization, template–monomer interactions, and growth kinetics of the polymer chains. The presence of a template molecule such as geraniol can locally disrupt or direct polymer growth, leading to the formation of heterogeneous surface features. These may manifest as variations in roughness, formation of nodular or globular structures, and the appearance of nanoscale depressions associated with the template removal. Therefore, AFM analysis provides indirect but highly valuable insights into the imprinting process by revealing how the presence of the template influences the polymer organization at the interface.

It is of importance to emphasize that, although the conceptual framework of molecular imprinting often describes the formation of well-defined cavities that are complementary in size and shape to the template molecule, direct visualization of individual binding sites by using AFM remains challenging nevertheless. The molecular dimensions of geraniol are on the order of a few nanometers, while the intrinsic roughness of electropolymerized Ppy films and the aggregation of polymer domains often occur at similar or larger length scales. Consequently, AFM does not typically resolve discrete, molecule-specific cavities. Instead, it provides an ensemble-averaged representation of the surface, where imprinting effects must be inferred from statistical and morphological changes rather than direct observation.

In practice, differences between MIP and NIP surfaces are commonly evaluated through comparative analysis of roughness parameters (e.g., root mean square roughness, R_q), height distribution profiles, and the surface feature uniformity [167]. MIP surfaces often exhibit an increased roughness and greater heterogeneity compared to NIP counterparts, thus reflecting the structural perturbations introduced by the template during polymer growth and its subsequent removal. In some cases, the presence of shallow depressions or irregular void-like features can be associated with imprinted regions;

however, these features cannot be unambiguously assigned to individual binding sites without complementary techniques.

Furthermore, AFM provides insights into the mechanical and structural stability of the polymer layers. Variations in the surface continuity, aggregation, or the presence of defects can indicate non-uniform polymerization or weak adhesion to the substrate, which are critical factors influencing the sensor performance. In electrochemically synthesized systems, such as Ppy-based MIPs, these morphological characteristics are directly linked to electrochemical behavior, including the charge transfer efficiency and accessibility of the binding sites.

Despite its limitations in resolving molecular-scale features, AFM remains an essential tool for MIP characterization because it bridges the gap between the nanoscale structure and the macroscopic sensor performance. When combined with techniques such as EIS and QCM, AFM contributes to a comprehensive structure–function analysis, allowing correlations to be established between the surface morphology, adsorption, and electrochemical response.

3.3.2. AFM methodology and data reliability

AFM measurements were performed by using a systematic reference–comparison approach so that to ensure reliable and reproducible interpretation of the surface morphology across different sample types. The analysis began with the characterization of bare gold substrates with the objective to establish a baseline topography and intrinsic roughness of the electrode surface. This was followed by sequential imaging of NIP, single-layer MIP, and double-layer MIP films, enabling a direct comparison of the morphological changes induced by polymer deposition and template incorporation.

Although imaging under liquid conditions was initially considered to replicate the operational environment of the sensor more closely, wet-mode measurements exhibited limited reproducibility. This was primarily due to instability in the tip–sample interactions, fluctuations in cantilever dynamics, and swelling or softening of the polymer layer in the solvent environment. These effects led to increased noise levels and a reduced image stability, making quantitative analysis unreliable. Therefore, all AFM measurements used for comparative and quantitative evaluation were conducted under dry conditions, where the imaging stability, resolution, and repeatability were significantly improved.

Measurements were carried out in the tapping (intermittent contact) mode, which is particularly suitable for soft polymeric materials, as it minimizes lateral forces and reduces the risk of surface deformation or

damage. This mode enables accurate reconstruction of surface features while preserving the native morphology of the Ppy films. The choice of the imaging mode is critical in MIP systems, where the polymer surface may contain both rigid and soft domains with varying mechanical properties.

To ensure consistency and comparability of the acquired data, all AFM images were processed by using the height channel as the primary source of quantitative information. Plane correction (median levelling) was applied to eliminate the sample tilt and scanner-induced vertical drift, thereby ensuring that height variations reflected true surface features rather than instrumental artifacts. Subsequently, height normalization was performed by setting the minimum height value to zero, thus allowing for direct comparison of vertical distributions across different samples.

Image artifacts, such as line defects caused by a temporary loss of the tip–sample contact or feedback instability, were corrected by using interpolation-based scar removal algorithms. This step was performed cautiously so that to preserve intrinsic morphological features while eliminating non-physical distortions. Such corrections are essential for accurate roughness analysis, particularly when evaluating nanoscale variations associated with imprinting effects.

The selection of representative scan areas was carried out with particular care. Regions affected by contamination, dust particles, or loosely bound polymer aggregates were excluded from analysis, as these features can artificially increase the roughness parameters and lead to misinterpretation of the surface heterogeneity. This consideration is especially important for polymer-based systems, where surface contamination can significantly distort statistical descriptors such as the root mean square roughness (R_q) and the average roughness (R_a).

Overall, the applied methodology ensures that the observed differences in the surface morphology between Au, NIP, and MIP systems are attributable to intrinsic structural characteristics rather than experimental artifacts. The combination of controlled imaging conditions, standardized data processing, and careful region selection provides a reliable basis for the subsequent quantitative and comparative analysis of imprinting effects at the nanoscale.

3.3.3. Morphological evolution of polymer layers

AFM analysis was performed with the intent to investigate the surface morphology associated with PPy film formation during electropolymerization. To minimize interference from the intrinsic grain structure of gold-coated QCM substrates, AFM imaging was conducted on films deposited on atomically flat mica substrates, which provide improved

visualization of the polymer topography. Therefore, the AFM observations primarily reflect qualitative differences in the polymer growth behavior rather than the exact morphology of the QCM sensor surfaces.

The NIP films exhibited relatively heterogeneous surface morphologies, characterized by irregular aggregates and pronounced height variations, which is consistent with less controlled polymer growth in the absence of a template. In contrast, polymerization performed in the presence of geraniol produced films with a more uniform surface organization and a reduced large-scale roughness, thereby suggesting that the template influenced the local polymer assembly during film formation.

The observed differences indicate that template-assisted electropolymerization affects the nanoscale organization of Ppy films and may contribute to the formation of more structurally ordered polymer architectures. However, because AFM characterization was performed on mica-supported films rather than directly on QCM sensor surfaces, and because imprint cavities were not directly visualized, the results should be interpreted as indirect morphological evidence of template effects during polymerization.

Overall, the AFM data support the conclusion that the presence of the template influences polymer growth behavior and surface organization, thus complementing the adsorption and electrochemical findings obtained from QCM and EIS measurements.

3.3.4. Quantitative roughness and height distribution analysis

Quantitative AFM analysis provided detailed insights into the structural differences between the investigated surfaces by evaluating the key roughness parameters, including the average roughness (S_a), root-mean-square roughness (S_q), total height (S_z), maximum valley depth (S_v), and surface skewness (S_{sk}). These parameters collectively describe both the amplitude and the distribution of surface features, enabling a more comprehensive interpretation of the polymer morphology beyond qualitative imaging (Figure 13).

The NIP control exhibited the highest S_a and S_q values, as well as the largest S_z variation, thus confirming its highly irregular and disordered morphology. The elevated S_z values indicate the presence of significant peak-to-valley differences, while reflecting uncontrolled polymer growth and aggregation. In addition, the strongly negative S_{sk} value suggests that the surface topography is dominated by deep depressions rather than symmetric height fluctuations. This asymmetry is indicative of structural instability and heterogeneous nucleation processes occurring in the absence of a template, where polymer chains grow without spatial constraints or directional organization.

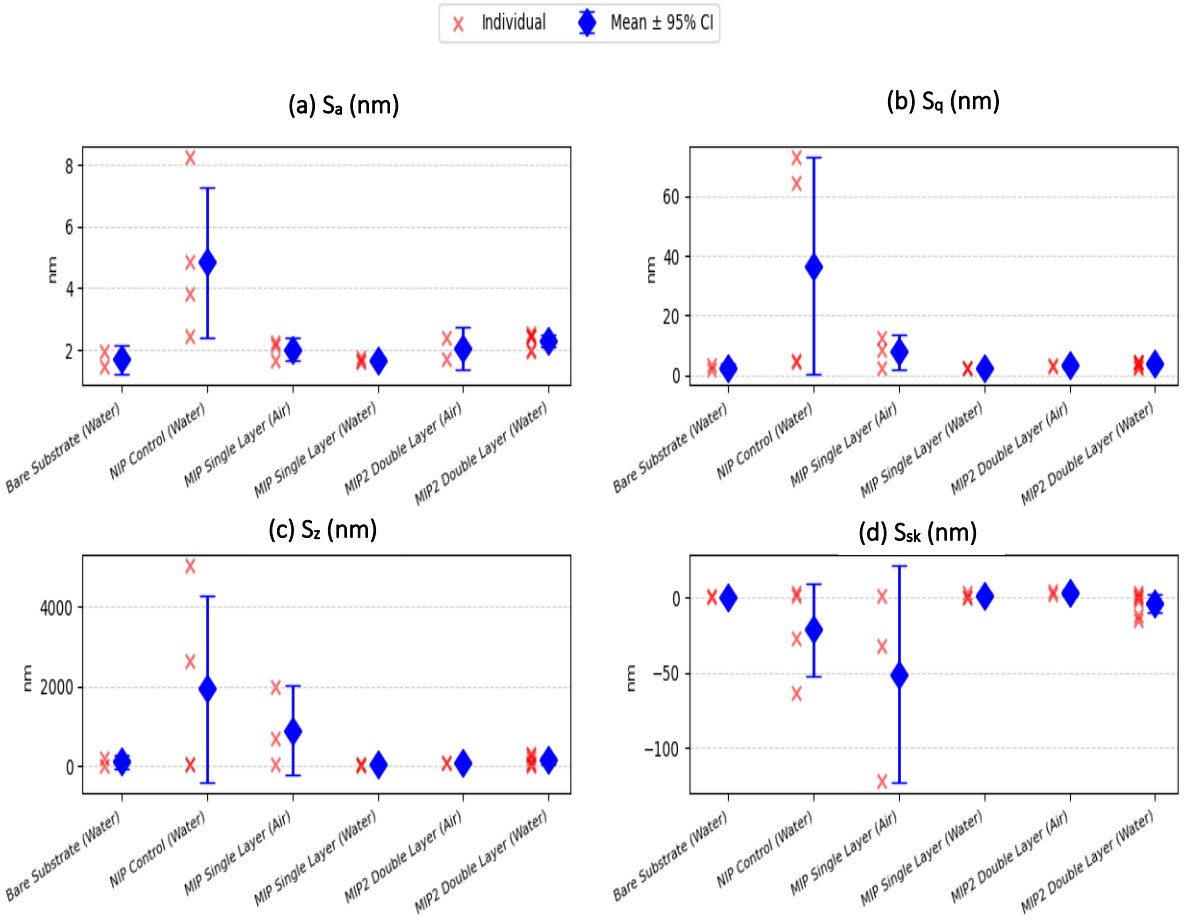

Figure 13. AFM roughness analysis for different surface parameters: (a) mean roughness (S_a), (b) root-mean-square roughness (S_q), (c) total height (S_z), and (d) surface skewness (S_{sk}) is shown for all sample groups. Individual measurement values are represented by red crosses, while the mean values with 95% confidence intervals are indicated by blue diamonds. The error bars represent the 95% confidence intervals of the mean values, and the noticeable overlap among several sample groups suggests strong measurement repeatability and precision of the roughness metrics

In contrast, the single-layer MIP displayed the lowest roughness values among all systems, thereby indicating the formation of a more uniform and compact polymer film. The reduction in the S_a and S_q values suggests that the presence of geraniol during electropolymerization promotes a more controlled growth process, likely by influencing the local monomer organization and limiting excessive aggregation. Despite this overall smoothness, the presence of measurable S_v confirms that nanoscale features are still present. These features can be attributed to imprinting effects, where the removal of template molecules leaves behind localized depressions within the polymer matrix.

The double-layer MIP exhibited intermediate roughness values but showed a significant increase in the S_v and S_z values compared to the single-layer system. This observation is particularly important, as it indicates that the double-layer architecture enhances the formation of deeper and more pronounced surface depressions. Unlike the NIP system, however, these features are not random, but, to the contrary, they appear as more localized and structurally defined elements. The presence of moderately negative skewness further supports this interpretation, suggesting a surface dominated by well-defined valleys associated with imprint-derived cavities rather than uncontrolled roughness.

From a mechanistic perspective, these results indicate a transition from disordered to structured heterogeneity. In the NIP system, high roughness and negative skewness arise from stochastic polymer growth and aggregation. In the single-layer MIP, the presence of a template suppresses large-scale irregularities, resulting in a smoother but still functionally modified surface. In the double-layer MIP, the combination of a stabilizing underlayer and template-directed polymerization leads to the formation of a more organized surface, where nanoscale depressions are more pronounced and likely correspond to accessible binding sites.

This distinction is critical for sensor performance. Random roughness, as observed in the NIP system, does not contribute effectively to selective recognition. In contrast, structured heterogeneity – characterized by defined depressions and controlled surface features – enhances analyte accessibility and binding specificity. The increased valley depth and controlled distribution of the surface features in the double-layer MIP therefore provide strong evidence for an improved imprinting efficiency and a higher density of functional recognition sites.

The statistical representation of roughness parameters (Figure 11), including individual data points and 95% confidence intervals, further confirms the reliability and reproducibility of the measurements. The overlap of confidence intervals between certain groups indicates consistent surface

characterization, while still allowing clear differentiation between polymer architectures. This statistical robustness supports the validity of the observed trends and strengthens the correlation between the surface morphology and the functional performance.

3.3.5. Correlation between AFM and EIS analysis

In order to complement the morphological analysis obtained by AFM, EIS was employed to evaluate the interfacial electrical properties of the polymer-modified electrodes and to provide additional insights into the surface structure and functionality (Table 6). While AFM offers direct information about the surface topography, EIS reflects the electrochemical activity of the interface, enabling the assessment of both the accessible surface area and the internal structural features that contribute to the charge storage and transfer.

A key parameter in this analysis is the double-layer capacitance, represented by the CPE_{dl} value. This parameter is commonly associated with the electrochemically active surface area and the ability of the interface to store a charge. In ideal systems, capacitance increases with the surface roughness due to the enlargement of the effective interfacial area. However, in real-life polymer systems, CPE_{dl} also reflects contributions from porosity, dielectric properties, and the distribution of surface heterogeneities.

Table 6. Parameters of the equivalent circuits obtained by performing the EIS fitting procedure

	CPE_{dl}, $\mu S \times s^{\alpha}$	α_{dl}	CPE_{ads}, $\mu S \times s^{\alpha}$	α_{ads}	R_{ct}, Ω
Au	53.0 ± 6.39	0.832 ± 0.016	-	-	-
single-layer MIP	72.5 ± 46.6	0.610 ± 0.073	308 ± 39.6	0.755 ± 0.021	62.3 ± 8.76
NIP	217 ± 102	0.647 ± 0.058	333 ± 75.9	0.852 ± 0.037	72.1 ± 13.2
double-layer MIP	1030 ± 193	0.571 ± 0.030	545 ± 180	1.00 ± 0.096	273 ± 68.9

The EIS results show that NIP exhibits a significantly higher CPE_{dl} compared to the single-layer MIP, which is consistent with the AFM observations of an increased surface roughness and structural disorder. The high roughness of NIP leads to an enlarged interfacial area, but this area is largely non-specific and poorly organized, as confirmed by its irregular morphology and high variability in the roughness parameters.

In contrast, the single-layer MIP demonstrates relatively low CPE_{dl} values, corresponding to its smoother and more compact surface observed in

AFM analysis. This suggests that, although imprinting introduces localized nanoscale features, the overall accessible surface area is reduced due to denser polymer packing and limited porosity. As a result, the electrochemical response is dominated by a relatively uniform but less accessible interface.

The most notable observation is that the double-layer MIP exhibits the highest CPE_{dl} values among all investigated systems, despite displaying a lower apparent roughness than NIP in AFM measurements. This apparent discrepancy highlights a fundamental difference between the morphological and electrochemical characterization techniques. While AFM primarily probes the outermost surface topography, EIS captures the total electrochemically active interface, including the internal porosity, subsurface cavities, and regions accessible to electrolyte ions but not directly visible in topographical imaging.

The elevated CPE_{dl} of the double-layer MIP therefore suggests the presence of a highly developed internal structure, consisting of nanoscale pores and interconnected pathways that increase the effective surface area. These features are likely associated with imprint-derived cavities and a more open polymer network formed under controlled growth conditions. The presence of the NIP underlayer plays a crucial role in this process by promoting uniform nucleation and reducing the direct substrate effects, thereby enabling the formation of a more porous and electrochemically accessible imprinted layer.

Additional insight is provided by the α_{dl} parameter, which reflects the degree of deviation from the ideal capacitive behavior. The lower α values, as observed for the double-layer MIP, indicate an increased surface heterogeneity and a broader distribution of time constants associated with the charge storage processes. This behavior is consistent with a complex interfacial structure containing a mixture of accessible pores, binding cavities, and heterogeneous domains.

Furthermore, the increased R_{ct} values observed for the double-layer MIP suggest that, despite its high capacitance, the polymer layer introduces a barrier to electron transfer. This is expected for thicker or more structured films, where an increased adsorption and analyte interaction can partially hinder charge transport. Importantly, this behavior reflects a trade-off between surface accessibility and electrical conductivity, which is characteristic of functional MIP systems.

Overall, the combined AFM and EIS analysis demonstrates that surface roughness alone is not a sufficient descriptor of the functional performance. While AFM provides valuable information on external morphology, EIS reveals the presence of internal structural features that critically influence

electrochemical behavior. The double-layer MIP system exhibits a transition from simple surface roughness to a hierarchically organized structure with an enhanced electrochemically active area and imprint-related porosity.

This complementary interpretation confirms that the double-layer architecture not only improves morphological uniformity but also enhances functional properties relevant to sensing, including charge storage, analyte accessibility, and interfacial responsiveness. Such structure–property relationships are essential for the rational design of high-performance MIP-based electrochemical sensors.

3.4. Translation and Commercialization of MIP-Based Geraniol Sensor

3.4.1. Translational context and relevance of MIP-based sensing

MIPs have emerged as a versatile class of synthetic recognition materials, characterized by a high chemical stability, low production cost, and robustness under harsh environmental conditions. Unlike biological recognition elements such as antibodies or enzymes, MIPs are resistant to variations in temperature, pH, and organic solvents, which makes them particularly attractive for applications beyond controlled laboratory environments. These properties position MIP-based sensors as promising candidates for real-world analytical systems, including environmental monitoring, food quality control, and industrial process analysis [123].

In a broader scientific context, the term *translation* refers to the process of converting fundamental research findings into practical, real-world applications. While the concept is most commonly associated with clinical sciences – —often referred to as *translational research*, where discoveries move from 'bench to bedside' – it has increasingly gained importance in materials science and sensor development [112,113]. In these fields, translation describes the pathway from proof-of-concept laboratory devices to robust, scalable, and commercially viable technologies. This transition has become a central focus over the past two decades, particularly with the rise of nanotechnology, advanced materials, and portable analytical systems.

Despite extensive research activity, the translation of MIP-based sensors into commercially available devices remains limited. Many studies report high sensitivity and selectivity under controlled experimental conditions; however, only a small fraction of these systems reach the stage of real-world implementation. This gap arises from several factors, including limited testing in complex matrices, insufficient long-term stability data,

challenges in reproducibility, and difficulties in integrating sensing materials into user-friendly analytical platforms.

Numerous examples illustrate this translational gap. MIP-based sensors have been successfully developed for compounds such as dopamine [168], bisphenol A [169], and atrazine [170], demonstrating excellent analytical performance in laboratory studies. Similarly, MIP systems targeting volatile organic compounds and EOs constituents – such as linalool or limonene – have been reported [152,171] . However, most of these systems remain at the prototype stage and are not commercially available, primarily due to challenges in device integration, stability under real-life conditions, and lack of standardized validation protocols.

In the specific case of geraniol and structurally related compounds, research is even more limited. While there are emerging reports of MIP-based sensing approaches for geranial and similar terpenoid molecules, these systems are typically demonstrated only under controlled laboratory conditions and have not yet been translated into deployable analytical devices [86,129]. This is partly due to the intrinsic complexity of essential oil matrices, where multiple structurally similar compounds coexist and compete for binding, thus making selective recognition significantly more challenging.

The absence of widely adopted MIP sensors for geraniol can be attributed to several factors. First, geraniol is a relatively small and flexible molecule, which complicates the formation of highly specific and structurally well-defined binding cavities. Second, its amphiphilic nature leads to a complex adsorption behavior at interfaces, as demonstrated in this study, which can interfere with controlled polymer formation. Third, analytical demand for geraniol-specific sensing has historically been addressed by using established techniques such as gas chromatography, reducing immediate pressure for sensor-based alternatives.

Nevertheless, structurally related compounds have been successfully incorporated into MIP systems for applications such as flavor analysis, environmental monitoring, and detection of adulterants in natural products. These studies demonstrate that terpenoid molecules can be effectively imprinted, although achieving high selectivity in complex mixtures still remains a major challenge. Importantly, many of these systems highlight the same limitations observed in the present work, including partial irreversibility of binding, matrix effects, and difficulties in achieving reproducible large-scale fabrication.

From a translational perspective, the present QCM-MIP system for geraniol contributes to addressing these challenges by combining detailed interfacial analysis with a rational design strategy. The introduction of a

double-layer architecture represents an important step toward improving reproducibility and structural control, which are key requirements for practical implementation. However, further work is required to advance this system beyond the proof-of-concept stage. Validation in real EOs matrices, evaluation of selectivity against structurally similar interferents, and integration into portable sensing platforms will be essential steps toward practical deployment.

Overall, while MIP-based sensing technologies have demonstrated strong potential, their successful translation into real-world applications still requires a shift in focus from purely analytical performance toward system-level considerations, including robustness, scalability, and usability. In this context, the development of MIP-based sensors for specific natural compounds – such as geraniol – represents not only a scientific challenge but also an opportunity to bridge the gap between advanced materials research and applied analytical technologies.

3.4.2. Translational Readiness Model as an evaluation framework

To systematically address the persistent gap between laboratory-scale sensor performance and real-world applicability, a *Translational Readiness Model* (TRM) was introduced as a conceptual evaluation framework for the developed QCM-MIP system. The TRM extends beyond the conventional analytical performance metrics – such as sensitivity, selectivity, and detection limit – by incorporating broader engineering and application-oriented criteria that determine whether a sensor can realistically transition from a research prototype to an operational device.

In a general sense, translational readiness refers to the degree to which a technology is prepared for deployment outside controlled laboratory conditions. While related to established frameworks such as *Technology Readiness Levels* (TRL), which are widely used in engineering and aerospace disciplines [172], the TRM applied here is adapted specifically for chemical sensing systems. It emphasizes not only technical maturity but also interfacial stability, reproducibility of fabrication, environmental robustness, and integration potential into portable analytical platforms.

The TRM is structured into several interdependent domains, each representing a key barrier in the translation pathway [173,174]. These include (i) interfacial stability and reproducibility of the sensing layer, (ii) performance consistency in complex and variable matrices, (iii) compatibility with miniaturized and portable readout systems, and (iv) scalability of material synthesis and device fabrication. Unlike purely performance-based

evaluation, this framework recognizes that even highly sensitive sensing platforms may fail in practical applications if structural or operational stability is deemed to be insufficient.

In the context of molecularly imprinted polymer systems, such as the geraniol-selective QCM sensor developed in this study, the TRM is particularly relevant. MIP performance is inherently dependent on nanoscale structural features formed during polymerization, which are highly sensitive to small variations in the synthesis conditions, template–monomer interactions, and interfacial adsorption phenomena. As demonstrated in the present work, factors such as competitive adsorption, polymer layer architecture, and interfacial charge transfer behavior directly influence not only the analytical response but also structural reproducibility.

Within this framework, the TRM is not applied as a rigid numerical scoring system, but rather as an interpretative tool for assessing system maturity. Experimental results obtained from QCM, CV, EIS, and AFM measurements are mapped onto TRM domains so that to identify which aspects of the system are sufficiently developed, and which remain limiting factors. For example, strong and reproducible interfacial adsorption supports translational progress in the stability domain, whereas partial irreversibility and matrix sensitivity highlight remaining challenges in operational robustness.

This approach allows the geraniol MIP sensor to be positioned within a broader development continuum, ranging from fundamental material characterization to application-ready sensing platforms. In this way, the TRM provides a structured bridge between mechanistic understanding and technological implementation, enabling a more realistic assessment of readiness for real-world analytical deployment.

3.4.3. Fabrication reproducibility and the role of polymer architecture

Fabrication reproducibility is one of the most critical limiting factors in the translational development of MIP-based sensors. Although electropolymerization of Ppy is widely used due to its simplicity, conductivity, and compatibility with aqueous and mixed solvent systems, it is inherently sensitive to small variations in electrochemical and interfacial conditions. Parameters such as monomer concentration, a potential window, scan rate, supporting electrolyte composition, and template distribution at the electrode surface can significantly influence nucleation dynamics and polymer growth pathways. As a result, even minor deviations in the synthesis

conditions may lead to substantial differences in the film morphology, thickness, porosity, and, ultimately, sensor response.

In this context, polymer formation should not be viewed as a purely deterministic deposition process, but, rather, as a coupled electrochemical–interfacial self-organization phenomenon. During CV, pyrrole oxidation generates radical cations that undergo coupling reactions, and the spatial distribution of these events is strongly influenced by local adsorption equilibria at the electrode interface. The presence of a template molecule such as geraniol further complicates this process by introducing competitive adsorption and spatial heterogeneity, which can distort monomer organization during early stages of film formation.

To mitigate these effects, the present work introduces a double-layer architecture as a rational strategy to improve fabrication reproducibility. The key concept behind this approach is the separation of interfacial functions into two distinct stages. First, a NIP underlayer is deposited to stabilize the electrode surface and establish a chemically and structurally uniform interface. This layer effectively reduces direct gold–solution interactions and minimizes the influence of surface heterogeneity during the subsequent polymer growth. Second, the molecularly imprinted layer is formed on top of this stabilized platform in the presence of the template molecule, allowing imprinting to occur under more controlled and reproducible interfacial conditions.

This architectural separation has important mechanistic consequences. The NIP base layer acts as an interfacial buffer which homogenizes charge distribution, reduces local variations in the electric field strength, and provides a more consistent nucleation environment for Ppy growth. At the same time, it limits uncontrolled adsorption of geraniol directly onto the gold surface, thereby reducing template-induced disruption of the monomer organization. As a result, the imprinting process becomes less dependent on stochastic surface effects and is more governed by bulk-controlled electrochemical parameters.

Experimental observations from QCM, AFM, and electrochemical analyses strongly support this interpretation. The double-layer system exhibited a more stable resonance frequency response, a reduced signal drift, and an improved reversibility during the adsorption–desorption cycles, thus indicating a more uniform and structurally coherent interfacial film comparing to a single-layer system. AFM measurements further confirmed a reduction in large-scale morphological heterogeneity, while preserving nanoscale features associated with the imprint formation. Collectively, these results suggest that

the double-layer architecture promotes a transition from uncontrolled surface growth toward a more regulated and reproducible polymerization regime.

From a translational standpoint, this improvement in structural consistency is particularly significant. In practical sensor applications, reproducibility is not defined solely by identical analytical performance under repeated measurements, but also by the ability to reliably reproduce sensor characteristics across independently fabricated devices. Although full statistical evaluation of batch-to-batch variation was not performed in this study, the observed reduction in the morphological and electrochemical variability indicates a clear improvement in fabrication robustness.

Therefore, the double-layer strategy represents more than a structural modification; it constitutes a fundamental design principle for improving the manufacturability of MIP-based electrochemical sensors. By decoupling surface stabilization from molecular imprinting, this approach directly addresses one of the key translational barriers in MIP technology – namely, the sensitivity of polymer formation to uncontrolled interfacial effects.

3.4.4. Analytical robustness and limitations in sensor performance

The analytical mechanism of the developed geraniol sensing system reflects a combination of strong molecular recognition and well-defined interfacial kinetics governed by heterogeneous binding phenomena typical for MIP. Kinetic analysis indicates that adsorption follows an apparent second-order regime, which reflects the coupled dependence on the analyte transport from the bulk solution and the availability of active binding sites within the polymer matrix. In contrast, desorption follows first-order kinetics, consistent with a unimolecular dissociation process in which the rate is governed by the stability of the pre-formed surface complexes rather than the concentration of the analyte in a solution. Collectively, these kinetic features indicate a non-ideal but structurally organized binding landscape composed of sites with different affinities and accessibility.

The extracted kinetic and association parameters, together with QCM-derived mass changes and EIS-derived interfacial responses, consistently demonstrate that the double-layer MIP exhibits the most pronounced interaction with geraniol. This enhanced response is attributed to the synergistic effect of a stabilized interfacial NIP underlayer and a more controlled imprinting environment, which, together, facilitate the formation of higher-affinity and more uniformly distributed recognition sites. The significant frequency shifts observed in QCM measurements, alongside pronounced variations in double-layer capacitance and charge-transfer

resistance, confirm that geraniol binding is accompanied not only by mass accumulation but also by a substantial reorganization of the electrode–electrolyte interface.

Despite these analytical characteristics, the system exhibits several limitations that directly influence its robustness. The most critical point is the partial irreversibility observed during desorption experiments, where the QCM signal does not fully return to the baseline. This indicates that a fraction of geraniol remains retained within the polymer matrix. Mechanistically, this process can be explained by a combination of diffusion-limited transport within deeper polymer regions, multilayer adsorption effects, and strong confinement within high-affinity imprinted cavities. Although such retention is often associated with strong binding performance, it simultaneously introduces signal hysteresis and reduces the regeneration efficiency.

A second limitation arises from the concentration regime used in this study. Experiments were conducted at relatively high analyte concentrations, which are appropriate for mechanistic characterization but may not fully represent application-relevant conditions. At lower concentrations, adsorption equilibria, the binding site occupancy, and signal-to-noise ratios may change significantly, thus potentially revealing transport limitations or reduced effective sensitivity that are not apparent under near-saturation conditions.

In addition, the absence of systematic interference studies represents a key gap in the current evaluation. EOs matrices typically contain structurally related terpenoids with similar physicochemical properties, which may compete for binding sites or contribute to nonspecific adsorption. In such environments, selectivity cannot be reliably inferred from single-analyte experiments alone, as competitive interfacial interactions may alter both binding dynamics and the signal response.

From a broader perspective, these observations highlight a fundamental trade-off inherent to MIP-based sensing systems: an increasing binding strength and imprinting fidelity enhances the analytical sensitivity but often reduces reversibility and regeneration performance. Accordingly, although the present system of the NIP/MIP architecture demonstrates strong analytical performance under controlled conditions, further optimization is required to balance affinity, reversibility, and long-term operational stability in contrast to a single-layer MIP-based system.

This balance is essential for ensuring reliable performance in real-world applications, where sensors must function under variable concentrations, complex chemical backgrounds, and repeated usage cycles without significant signal degradation.

Within this context, the analytical robustness and limitations identified in this study directly inform the TRM evaluation of the system. In this framework, the adsorption strength, kinetic mechanism, reversibility, and the resistance to matrix effects correspond to key domains of the functional performance stability and operational reliability. The strong and reproducible interfacial responses observed in QCM and EIS analyses indicate a high level of maturity in the recognition and signal generation domains. However, the observed desorption hysteresis, concentration dependence, and lack of validation in complex matrices indicate that the system has not yet achieved full readiness in regeneration performance and real-world applicability.

From a TRM perspective, the developed prototype of a NIP/MIP architecture is therefore positioned at an intermediate stage of translational maturity. It demonstrates clear proof-of-functionality under controlled laboratory conditions, while being supported by consistent electrochemical–gravimetric correlations and stable interfacial response. At the same time, the identified limitations define the remaining barriers that must be addressed prior to application-level deployment.

Importantly, the TRM framework allows these findings to be interpreted as interconnected consequences of the same underlying mechanism: strong template–polymer interactions that enhance sensitivity while simultaneously limiting reversibility. This intrinsic coupling represents a central design constraint in molecular imprinting systems and is a key determinant of their translational behavior.

Consequently, the present analytical robustness analysis not only characterizes the sensor performance but also defines its position within the broader translational development pathway. This provides a structured foundation for future optimization strategies aimed at improving regeneration efficiency, expanding matrix validation, and enhancing environmental robustness while preserving high-affinity molecular recognition.

3.4.5. Matrix compatibility and selectivity challenges

The selectivity limitations discussed in the previous section can be directly rationalized through the interfacial mechanisms established earlier by adsorption studies, QCM, and EIS analysis. Across these techniques, a consistent picture emerges in which geraniol exhibits strong but non-exclusive interactions with the polymer interface, governed by a combination of specific imprint recognition and nonspecific surface adsorption.

From the adsorption and QCM results, it was demonstrated that geraniol possesses a measurable affinity toward both Au and Ppy surfaces, with evidence of competitive adsorption against pyrrole during polymer formation. This competition is not only a fabrication phenomenon but also a fundamental indicator of the system's interfacial selectivity. The fact that geraniol can effectively occupy active surface sites prior to and during polymer growth suggests that its binding is not strictly limited to imprinted cavities but also involves broader hydrophobic and weakly polar interactions with the polymer matrix. Consequently, in complex matrices, structurally related terpenoids are expected to exhibit a similar interfacial response, leading to a partial overlap in the adsorption pathways.

This interpretation is further supported by the QCM measurements, which revealed a significant mass uptake for geraniol and incomplete reversibility during desorption. The residual frequency shift observed after regeneration indicates that a fraction of molecules remains trapped within the polymer structure, either in high affinity imprinted cavities or in non-specific adsorption domains. Importantly, such kinetically slow or partially irreversible binding sites are not inherently selective; rather, they reflect a distribution of interaction strengths across the polymer surface. In a multi-component system, these same sites may accommodate competing analytes with comparable physicochemical properties, thereby reducing effective selectivity.

EIS analysis provides complementary evidence for this interfacial complexity. The observed changes in double-layer capacitance and charge-transfer resistance upon geraniol exposure confirm that adsorption is not confined to discrete recognition sites, but, instead, that it induces a broader reorganization of the electrode–electrolyte interface. The magnitude of these changes depends strongly on the polymer architecture, with the double-layer MIP showing the most pronounced response. While this indicates an enhanced sensitivity, it also implies a highly reactive and structurally dynamic interface, which may respond to multiple chemically similar species in a comparable manner.

Taken together, these findings suggest that selectivity in the present system is not solely governed by the classical 'lock-and-key' cavity recognition but rather emerges from a combination of imprinted site binding, nonspecific adsorption, and interfacial charge redistribution effects. In simplified solutions, these contributions collectively produce a strong and well-defined analytical signal for geraniol. However, in complex matrices, the same mechanisms may be simultaneously activated by structurally related compounds, leading to signal convolution and a reduced specificity.

Therefore, the selectivity challenge identified in biofluid and real-sample contexts is not an isolated limitation, but, to the contrary, a direct consequence of the adsorption and interfacial processes observed in QCM and EIS experiments. This mechanistic continuity highlights that improvements in selectivity will require not only optimization of the cavity formation, but also suppression of nonspecific interfacial adsorption pathways and a better control of polymer–solution interactions at the electrode surface.

3.4.6. Manufacturability, scalability, and system integration

From a scalability perspective, electropolymerization is nevertheless a favorable technique because it is directly compatible with a wide range of electrode architectures, including miniaturized and patterned systems. Translation toward screen-printed electrodes or microfabricated gold arrays would allow parallelized fabrication while maintaining control over interfacial polymer growth. Importantly, the polymer chemistry itself does not require expensive reagents, and both pyrrole and geraniol are readily available, thus suggesting that the material cost is not a limiting factor. Instead, the main barrier lies in the process reproducibility – specifically, in ensuring that the same interfacial conditions (monomer adsorption, template distribution, and nucleation behavior) are consistently reproduced across multiple devices.

This issue directly connects to the mechanistic understanding developed in the adsorption, QCM, and EIS sections. As demonstrated above, the sensing performance is highly sensitive to the initial interfacial state prior to polymer growth, where competitive adsorption between geraniol and pyrrole determines nucleation density and film uniformity. Therefore, any scaled-up fabrication strategy must preserve control over these early-stage adsorption equilibria. Without such control, variations in the surface coverage would propagate into differences in the polymer morphology, binding site distribution, and, ultimately, in the sensor response variability. In this sense, manufacturability is not only a technical scaling issue but also a direct extension of the adsorption-controlled growth mechanism identified experimentally.

System integration represents a second, equally important translational challenge. In the present work, QCM and EIS were employed as complementary analytical platforms to resolve mass loading and interfacial charge-transfer phenomena with high sensitivity. However, both techniques in their standard laboratory configuration require relatively complex instrumentation, including frequency tracking electronics, potentiostats, and controlled fluidic systems. While these tools are invaluable for mechanistic

characterization, they are not directly optimized for portable or field-deployable devices. Therefore, future integration would likely require a simplification of readout strategies, potentially through single-transduction modes (e.g., impedance-only or frequency-only sensing), or through integration into compact electrochemical chips with miniaturized electronics.

Despite these limitations, the strong and reproducible interfacial responses observed across QCM, EIS, and kinetic analyses indicate that the underlying sensing mechanism is inherently compatible with miniaturization. The same adsorption-driven processes that govern frequency shifts and impedance changes at the laboratory scale can, in principle, be translated into simplified electronic signals in a device format, if the electrode architecture and polymer growth conditions are sufficiently standardized.

Overall, manufacturability and system integration considerations reinforce a key conclusion emerging from the mechanistic sections: the performance of the system is fundamentally governed by interfacial adsorption phenomena. This means that a successful scale-up is not only a question of device engineering but also of preserving the same adsorption-controlled polymer formation pathway that defines sensor functionality at the laboratory level.

3.4.7. Overall translational perspective and future directions

The results of this study demonstrate that the developed geraniol-selective MIP sensor exhibits strong analytical performance, supported by consistent QCM, EIS, and AFM evidence. Across all techniques, a coherent picture emerges, in which, the sensor response is governed by interfacial adsorption processes strongly dependent on the polymer architecture, particularly, on the introduction of a double-layer configuration.

From a quantitative standpoint, QCM measurements revealed a marked difference in adsorption capacity between single-layer and double-layer MIP systems. At 0.05 $mol \cdot L^{-1}$ geraniol, the double-layer MIP produced a frequency shift of approximately −34 Hz, corresponding to a mass uptake of ~602 ng (3.0×10^{-6} $g \cdot cm^{-2}$), whereas the single-layer system showed only ~24 ng. This translates to a molecular loading on the order of ~2.35×10^{15} molecules and a surface density of ~10^{16} $molecules \cdot cm^{-2}$, indicating not only strong adsorption but also possible multilayer accumulation or penetration into the polymer network. This is consistent with the partial irreversibility observed during desorption.

Kinetic modelling further supports this interpretation. Adsorption follows an apparent second-order regime, reflecting coupled dependence on

the analyte transport and available binding sites, while desorption follows first-order kinetics governed by complex stability. The highest K_{asoc} was observed for the double-layer MIP, thus confirming that structural modification enhances the overall binding affinity. However, incomplete desorption indicates diffusion limitations and heterogeneous binding environments, which improve the sensitivity but reduce the regeneration efficiency.

EIS analysis provides complementary evidence of interfacial restructuring. Exposure to geraniol leads to a decrease in double-layer CPE_{dl}, most strongly in the double-layer MIP (≈2.5-fold reduction), thus indicating a significant rearrangement of the electrical double layer. In contrast, NIP and single-layer systems show weaker responses (~1.4-fold). These changes confirm that adsorption is not purely surface-localized, but that it affects the entire interfacial charge distribution. The relatively high baseline capacitance of the double-layer MIP further suggests an increased electrochemically active area, likely due to nanoscale porosity.

AFM results clarify the structural origin of these effects. While the NIP exhibits the highest roughness and uncontrolled morphology, the double-layer MIP shows moderate roughness but significantly deeper and more defined depressions. These features are consistent with imprint-derived cavities rather than random surface irregularities, supporting the formation of structurally functional binding domains.

Overall, the data demonstrate that the polymer architecture governs both the morphology and the electrochemical response. The NIP underlayer stabilizes the film growth, reduces the interfacial disorder, and enables a more controlled imprint formation in the upper layer, leading to an improved reproducibility and stronger analyte binding.

Despite these advantages, several limitations remain. Most importantly, partial irreversibility of adsorption may limit the regeneration efficiency and long-term operational stability. In addition, although the sensor was tested by using real EOs samples, most experiments were still performed in simplified molecular systems. Therefore, sensor performance in more complex real-world matrices remains insufficiently validated, which represents one of the major challenges in the field of molecularly imprinted sensors.

Furthermore, selectivity studies remain limited, particularly regarding the sensor response toward structurally similar or potentially interfering compounds. Such investigations are essential for evaluating the practical applicability under realistic analytical conditions. Additional studies are also required to better assess the long-term stability, reproducibility, and robustness under varying operational conditions. Although the proposed

structure is presented as an improvement, evidence demonstrating stable performance over extended periods is still limited.

Another potential limitation is template leakage, where residual template molecules remaining within the polymer matrix may influence measurement accuracy. In some cases, electrochemical signals may also be affected by non-specific surface processes, which could contribute to signal distortion and complicate the interpretation of the analytical response.

Reproducibility and scalability likewise require further development. Although electropolymerization is compatible with scalable fabrication approaches, the current manual workflow restricts the throughput. Transition toward standardized or printed electrode platforms will therefore be important for the practical deployment and wider application.

Nevertheless, the system demonstrates a clear translational potential. The double-layer MIP architecture significantly improves the adsorption capacity, binding strength, and interfacial stability compared to the conventional designs. Beyond sensing, the strong retention of geraniol suggests possible applications in selective capture or controlled release systems, although this remains at an exploratory level. Importantly, the limitations discussed above – including selectivity toward interfering compounds, performance in complex real-world matrices, long-term stability, reproducibility, template leakage, and the influence of non-specific surface processes – represent important directions for future research and will be systematically investigated in subsequent studies to further validate the practical applicability of the proposed sensing platform.

In summary, this work establishes a mechanistic link between interfacial adsorption, polymer architecture, and analytical performance. It shows that improved sensing characteristics arise from the same strong template–polymer interactions that also introduce limitations in reversibility. Addressing this trade-off will be central to future optimization. The double-layer strategy therefore represents an important step toward more robust, scalable, and application-ready MIP-based sensing platforms.

CONCLUSIONS

1. A geraniol adsorption mechanism on gold sensor surfaces has been successfully investigated. The results demonstrated that geraniol exhibits strong affinity for the electrode surface, which significantly influences the formation and uniformity of the subsequent polymer layers. This observation highlights the importance of understanding template–surface interactions in the design of molecularly imprinted polymer systems.
2. Molecularly imprinted polypyrrole layers have been developed and optimized based on adsorption. A double-layer strategy, consisting of a NIP base layer followed by an imprinted layer, improved the polymerization stability and ensured a more controlled formation of recognition sites, even when relatively high concentrations of geraniol were used.
3. The morphology and structural properties of the polymer layers have been characterized by using AFM. These analyses confirmed the formation of continuous, uniform polymer layers and provided insights into the layer thickness and surface topography. Although individual molecular cavities could not be directly visualized, the measurements support the successful formation of structured polymer films influenced by template adsorption.
4. The feasibility of the developed system as a prototype electrochemical sensor has been evaluated. The study demonstrates that the constructed MIPs system can respond to geraniol and establishes a foundation for further optimization. Additionally, the work highlights potential opportunities for translating the laboratory-scale sensor into practical analytical or consumer-oriented devices.

Santrumpos

AJM – atominės jėgos mikroskopija
CV – ciklinė voltamperometrija
EA – eteriniai aliejai
EIS – elektrocheminio impedanso spektroskopija
MIP – molekulių įspaudais modifikuoti polimerai
MIT – molekulinio įspaudimo technologija
NIP – neįspaustas polimeras
Ppy – polipirolas
KM – kvarcinės mikrosvarstyklės

Įvadas

Pastaraisiais metais moksliniuose tyrimuose vis daugiau dėmesio skiriama natūralių produktų ir augalinės kilmės junginių analizei, nes šios medžiagos pasižymi dideliu biologiniu aktyvumu ir potencialiu pritaikymu farmacijos, kosmetikos bei biomedicinos srityse [10].

Ypač svarbi natūralių junginių grupė yra eteriniai aliejai (EA), kurie yra sudėtingi lakūs biologiškai aktyvių komponentų mišiniai. Šie junginiai pasižymi antimikrobiniu, priešuždegiminiu, antioksidaciniu ir net priešvėžiniu poveikiu [2–4]. Tačiau jų sudėtinga sudėtis ir cheminis nestabilumas kelia nemažų analitinių sunkumų, ypač siekiant užtikrinti kokybės kontrolę, autentiškumą ir tikslų dozavimą.

Tradiciniai analitiniai metodai, tokie kaip dujų chromatografija ir superkritinių skysčių chromatografija, yra tinkami EA analizei, nes yra tikslūs, tačiau eksperimentas ilgas, o norint jį atlikti reikia sudėtingos įrangos ir ja naudotis mokančių darbuotojų [13]. Dėl šių apribojimų vis daugiau dėmesio skiriama alternatyviems, greitiems ir nešiojamiems jutikliams, galintiems veikti realiu laiku [14]. Nepaisant technologinės pažangos, išlieka esminė problema – kaip sukurti selektyvius, paprastus ir ekonomiškus jutiklius, kuriuos būtų galima naudoti sudėtingose matricose.

Šio tyrimo hipotezė – molekulių įspaudais modifikuoti (MIP) polipirolo (Ppy) sluoksniai, susidarę ant elektrocheminių jutiklių paviršių, gali selektyviai atpažinti geraniolio molekules dėl specifinių molekulinių sąveikų.

Siekiant patikrinti šią hipotezę, buvo suformuluoti šie uždaviniai:

1. Ištirti geraniolio adsorbcijos mechanizmą ant auksinių kvarcinių mikrosvarstyklių (KM) jutiklio paviršių ir įvertinti jos įtaką polimerinio sluoksnio susidarymui.
2. Sukurti ir optimizuoti MIP polipirolo sluoksnius, taikant elektrocheminę polimerizaciją.
3. Apibūdinti sukurtų polimerinių sluoksnių morfologiją ir struktūrines savybes, naudojant atominės jėgos mikroskopiją.
4. Įvertinti sukurtos sistemos, kaip elektrocheminės geraniolio aptikimo platformos prototipo, veikimą ir nustatyti jos pritaikymo praktikoje potencialą.

Ginamieji teiginiai

1. Geraniolio adsorbcija ant aukso elektrodo paviršiaus keičia elektrocheminę pirolo polimerizacijos eigą ir tiesiogiai veikia molekuliniu būdu įspaustų polipirolo sluoksnių struktūrinę organizaciją, tarpfazines savybes bei augimo dinamiką.
2. Dvisluoksnė MIP architektūra reikšmingai padidina adsorbcinę gebą ir tarpfazinį persitvarkymą – palyginti su vienasluoksnėmis sistemomis, adsorbuota masė padidėja apytiksliai 25 kartus (~ 602 ng ir ~ 24 ng), o dvigubo elektrinio sluoksnio talpa sumažėja apie 2,5 karto.
3. KM ir elektrocheminio impedanso spektroskopijos (EIS) analizė parodė, kad geraniolio adsorbcija sukurtose MIP sistemose yra difuzijos valdoma ir iš dalies negrįžtama, apimanti tiek paviršinį prisijungimą, tiek skverbimąsi į polimerinį tinklą, o apskaičiuotas paviršiaus tankis siekia ~ 10^{16} molekulių·cm^{-2}.
4. Atominės jėgos mikroskopijos (AJM) analizė patvirtino ištisinių ir morfologiškai skirtingų polimerinių sluoksnių susidarymą, o sukurta elektrocheminė MIP platforma užtikrina selektyvų geraniolio atpažinimą eterinių aliejų sistemose ir parodo hidrofobinių aromatinių junginių jutiklių kūrimo potencialą.

Mokslinis naujumas

Šio darbo mokslinį naujumą sudaro tai, kad išaiškintas geraniolio ir Ppy sąveikos mechanizmas ir nustatyta jo įtaka MIP sluoksnių sudarymui. Nors dvisluoksnės MIP / neįspausto polimero (NIP) architektūros ir Ppy pagrindu sukurti elektrocheminiai jutikliai jau buvo tiriami ankstesniuose darbuose,

šiame tyrime pateikiami keli originalūs aspektai, susiję su tiksliniu analitės pasirinkimu ir supratimu apie polimero sluoksnių susidarymą.

Šiame darbe jutiklis buvo specialiai sukurtas eterinių aliejų komponentui – geranioliui – aptikti. Geraniolis iki šiol yra mažai ištirtas junginys elektrocheminių MIP sistemų srityje. Mokslinės literatūros ir duomenų bazių analizė rodo, kad elektrocheminių MIP jutiklių, skirtų geranioliui aptikti, yra labai nedaug. Viena pagrindinių to priežasčių – hidrofobinių EA junginių aptikimo sudėtingumas, nes šios medžiagos pasižymi mažu tirpumu vandeninėje terpėje ir dažniausiai analizuojamos organinių tirpiklių sistemose. Tai riboja įprastų jutiklių praktinio pritaikymo galimybes ir apsunkina selektyvių jutimo platformų kūrimą tokioms analitėms.

Geraniolio pasirinkimas kaip tikslinės molekulės yra svarbus ir dėl jo reguliavimo bei toksikologinių ypatumų. Pastaraisiais metais geranioliui skiriama vis daugiau dėmesio, nes pagal Europos Sąjungos (ES) kosmetikos reglamentus jis priskiriamas reguliuojamiems kvapiųjų medžiagų alergenams, aptinkamiems aromaterapijos ir kosmetikos produktuose. Pagal galiojančius ES reikalavimus, tokie kvapiųjų medžiagų alergenai kaip geraniolis turi būti atskirai nurodomi kosmetikos gaminių etiketėse, kai jų koncentracija viršija 0,001 % nenuplaunamuose produktuose ir 0,01 % – nuplaunamuose produktuose. Be to, naujausiais Reglamento 1223/2009 pakeitimais reguliuojamų kvapiųjų medžiagų alergenų sąrašas buvo išplėstas nuo 26 iki daugiau nei 80 medžiagų, taip atspindint stiprėjantį reguliacinį dėmesį alergizuojančioms aromatinėms medžiagoms.

Tyrimo metu buvo nustatyta, kad geraniolis ne tik adsorbuojasi ant aukso elektrodo paviršiaus, bet ir aktyviai veikia pirolo elektrocheminės polimerizacijos kinetiką. Dėl to tiesiogiai kinta susidarančio MIP sluoksnio struktūra ir storėjimo greitis. Šie rezultatai rodo, kad ši analitė veikia ne kaip pasyvus įspaudus formuojantis faktorius, bet daro įtaką aktyviam struktūriniam polimero formavimui elektropolimerizacijos metu.

Taip pat buvo pasiūlyta ir eksperimentiškai patvirtinta dvisluoksnė NIP/MIP architektūra, pasižyminti geresniu elektrodo ir polimero sąsajos stabilumu, mažesniu struktūrinių defektų kiekiu ir didesniu jutimo sluoksnio atkuriamumu, palyginti su įprastomis vienasluoksnėmis sistemomis.

Be to, buvo sukurta integruota charakterizavimo metodologija, apimanti CV, EIS, KM ir AJM metodus. Ši multimodalinė metodika leidžia išsamiai įvertinti elektrocheminius procesus, masės pokyčius ir paviršiaus morfologiją MIP sluoksnių susidarymo metu.

Apibendrinant – gauti rezultatai suteikia naujų žinių apie mažų organinių molekulių, tokių kaip geraniolis, dvejopą vaidmenį molekulinio

įspaudimo procesuose – jos veikia ne tik kaip tikslinės analitės, bet ir kaip aktyvūs struktūriniai moduliatoriai, lemiantys jų aptikimo funkcines savybes.

Literatūros apžvalga

MIP analitinėse sistemose. Vienas perspektyviausių sprendimų selektyviam atpažinimui yra MIP, kurie pastaraisiais dešimtmečiais tapo svarbia sintetinės analitinės chemijos kryptimi [20–22]. MIP veikia kaip dirbtiniai receptoriai [19], imituojantys biologinių sistemų, tokių kaip antikūnai ar fermentai, selektyvumą, tačiau pasižymintys didesniu cheminiu ir terminiu stabilumu.

MIP struktūra formuojama polimerizacijos metu, kai funkciniai monomerai sąveikauja su šablonine molekule ir sudaro kompleksą [26]. Literatūroje pabrėžiama, kad MIP savybės labai priklauso nuo monomerų pasirinkimo, kurie lemia sąveikų pobūdį – vandenilinius ryšius, elektrostatines ar hidrofobines sąveikas – pasirinkimo [32]. Šie komponentai reguliuoja sąveikų stiprumą, poringumą, struktūros standumą ir analitinių vietų prieinamumą, todėl yra kritiškai svarbūs jutiklio jautrumui ir selektyvumui. Po polimerizacijos ir šablono pašalinimo lieka ertmės, komplementarios tiksliniam junginiui. Šios ertmės užtikrina selektyvų atpažinimą [28]. Molekulinis įspaudimas gali būti kovalentinis, nekovalentinis arba pusiau kovalentinis, tai priklauso nuo sąveikos tipo, o dažniausiai taikomas nekovalentinis metodas dėl paprastumo ir universalumo. Pastaraisiais metais ypač išpopuliarėjo paviršinis įspaudimas, kuris leidžia pagreitinti analičių prisijungimą ir pagerinti jutiklių atsako laiką.

MIP gali būti pritaikyti biožymenims aptikti, vaistų pernašos sistemose ir biojutikliuose. Ypač svarbus jų pritaikymas sudėtingose biologinėse matricose, kur tradiciniai receptoriai dažnai praranda selektyvumą. Tačiau vienas didžiausių keblumų yra heterogeniškų jungimosi vietų susidarymas ir nepakankamas standartizavimas [48].

Eteriniai aliejai. EA yra sudėtingi, lakių ir lipofilinių junginių mišiniai, sudaryti iš daugelio chemiškai skirtingų komponentų, daugiausia monoterpenų ir fenilpropanoidų [1]. Jų cheminė sudėtis labai priklauso nuo augalo rūšies, geografinių sąlygų ir ekstrakcijos metodų, todėl jie pasižymi dideliu kintamumu [70]. EA aptinkami cheminiai junginiai, veikiami aplinkos veiksnių, lengvai oksiduojasi, garuoja ir palaipsniui degraduoja [68]. Dėl to jų analitinis stabilumas yra ribotas. Be to, jų sudėtyje esantys struktūriškai panašūs junginiai apsunkina selektyvią analizę, ypač kai reikia atskirti izomerus ar artimus analogus [71,72].

Šie keblumai skatina kurti pažangius analizės metodus, leidžiančius selektyviai aptikti individualius EA komponentus. MIP yra perspektyvus

sprendimas, nes leidžia sukurti selektyvias konkrečių junginių atpažinimo vietas net sudėtinguose mišiniuose. Tai ypač svarbu kokybės kontrolei ir farmaciniam taikymui. Svarbu pabrėžti, kad EA lipofilinės savybės lemia jų stiprią sąveiką su paviršiais, o tai gali padidinti adsorbciją, bet kartu sukelti nespecifinį prisijungimą. Todėl būtina kruopščiai optimizuoti jutiklių paviršius ir naudoti selektyvias atpažinimo sistemas.

Geraniolis. Geraniolis pasirinktas kaip pagrindinis šio darbo metu kurtos MIP sistemos komponentas dėl savo aiškios struktūros, biologinio aktyvumo ir paplitimo įvairiuose EA [81]. Jis pasižymi antioksidaciniu [5], priešuždegiminiu [5], antimikrobiniu [8,82] ir priešvėžiniu poveikiu [6,7,9], todėl plačiai tiriamas farmacijos srityje.

Struktūriškai geraniolis – tai aciklinis monoterpeno alkoholis, turintis hidroksilo grupę, kuri leidžia sudaryti vandenilinius ryšius su MIP monomerais [83]. Tai ypač svarbu formuojant stabilų MIP analitės ir monomero kompleksą. Tačiau geraniolis turi ir struktūriškai panašių junginių, kaip antai nerolis, todėl užtikrinti selektyvumą yra sudėtinga [85]. Dėl to reikalingas tikslus MIT proceso optimizavimas.

Polimerinės medžiagos ir polipirolo sistemos. Polimerinės medžiagos yra esminė MIT, vaistų tiekimo sistemų ir elektrocheminių jutiklių kūrimo dalis dėl jų struktūrinio lankstumo ir galimybės valdyti morfologiją, poringumą bei chemines savybes. Šios savybės leidžia kurti selektyvias ir efektyvias analitines sistemas [88]. Tarp įvairių polimerų ypatingas dėmesys skiriamas laidiesiems polimerams, ypač Ppy, kuris plačiai naudojamas elektrocheminiuose jutikliuose ir MIP sistemose. Ppy pasižymi paprasta sinteze, geru cheminiu stabilumu, biologiniu suderinamumu ir gebėjimu formuoti vienalyčius sluoksnius ant elektrodų paviršių [92]. Jo struktūra leidžia sąveikauti su tikslinėmis molekulėmis per vandenilinius ryšius, elektrostatines bei π–π sąveikas, o tai yra svarbu selektyvių įspaudimo vietų formavimui [91]. Elektropolimerizacija leidžia tiksliai kontroliuoti Ppy sluoksnio storį, struktūrą ir nusodinimą tiesiogiai ant elektrodo paviršiaus, užtikrinant gerą sukibimą ir pakartojamumą. Be to, šis metodas leidžia tiesiogiai įterpti šablonines molekules polimerizacijos metu, taip supaprastinama jutiklių gamyba.

Palyginti su kitais monomerais, pavyzdžiui, metakriline rūgštimi, akrilamidu, stirenu, polianilinu ar polidopaminu, Ppy pasižymi optimaliu fizikinių-cheminių savybių balansu. EA analizėje polimero pasirinkimas yra ypač svarbus dėl tikslinių junginių hidrofobiškumo ir struktūrinės įvairovės. Polimeras turi užtikrinti pakankamą sąveiką su analite.

Jutiklio sistemos koncepcija.

Jutiklio sistema šiam darbui buvo kuriama remiantis poreikiu selektyviai aptikti geraniolį sudėtingose EA matricose. Dėl tokių analitinių veiksnių kaip mažas tirpumas vandenyje, struktūrinis junginių panašumas ir galimi trukdžiai pasirinktas MIP kartu su elektrocheminiu signalo nuskaitymu.

Pagrindinis jutiklio veikimo principas grindžiamas MIP, suformuotu iš Ppy, kuris elektropolimerizuojamas tiesiai ant elektrodo paviršiaus. Šitaip sukuriamos selektyvios atpažinimo ertmės, komplementarios geraniolio molekulei. Analitinis signalas registruojamas taikant EIS metodą, kuris leidžia stebėti krūvio pernašos varžos ir dvigubo sluoksnio talpos pokyčius, atsirandančius dėl analitės prisijungimo.

Papildomai jutiklio veikimo ir struktūros analizei buvo taikomi KM ir AJM metodai. KM leido realiu laiku stebėti masės pokyčius adsorbcijos metu, o AJM padėjo suprasti paviršiaus morfologiją ir polimero sluoksnio struktūrą.

Ši kelių metodų strategija leidžia susieti jutiklio struktūrines savybes su jo funkciniu atsaku ir taip užtikrinti išsamesnį supratimą apie molekulinio atpažinimo mechanizmus. Tokia koncepcija sudaro pagrindą selektyvių ir jautrių jutiklių, tinkamų realioms analitinėms sąlygoms, kūrimui.

Transliacinis potencialas. Nors MIP pagrindu sukurti jutikliai laboratorinėmis sąlygomis pasižymi geromis analitinėmis savybėmis, jų perkėlimas į realias taikymo sritis tebėra sudėtingas. Pagrindinės kliūtys susijusios su prietaisų integracija, stabilumu aplinkos sąlygomis ir gamybos mastelio didinimu. Transliacinis procesas apima ne tik jautrumo ir selektyvumo optimizavimą, bet ir pakartojamumo užtikrinimą, veikimą sudėtingose matricose, bei integraciją į patogias naudoti sistemas.

Praktiniam pritaikymui būtina integruoti jutiklį su kompaktiška elektronika, tokia kaip miniatiūriniai potenciostatai ar KM valdymo sistemos, taip pat užtikrinti duomenų perdavimą realiu laiku. Nors vyksta technologinė pažanga, dauguma MIP jutiklių vis dar yra prototipo stadijos dėl riboto stabilumo, sudėtingos standartizacijos ir integracijos problemų. Todėl tolesni tyrimai turi būti orientuoti į veikimą realiose eterinių aliejų matricose ir įrenginių pritaikymą praktinėms sąlygoms.

MIP trūkumai ir ateities perspektyvos. Nepaisant MIP technologijos pranašumų, lieka daug svarbių trūkumų, ypač dirbant su sudėtingomis sistemomis, tokiomis kaip EA. Vienas pagrindinių sunkumų – selektyvumo užtikrinimas esant struktūriškai panašiems junginiams, kurie gali sukelti interferenciją. Taip pat svarbūs veiksniai yra aplinkos sąlygų įtaka, paviršiaus užsiteršimas, nevisiškas šablono pašalinimas ir signalų nestabilumas.

Papildomų problemų kyla dėl riboto pakartojamumo tarp skirtingų polimerų partijų ir standartizuotų sintezės metodų trūkumo. Šie aspektai riboja MIP jutiklių taikymą reguliuojamose srityse.

Ateities tyrimai turėtų būti orientuoti į jutiklių integraciją į nešiojamas sistemas, pažangių medžiagų (pvz., nanostruktūrų ar hibridinių kompozitų) taikymą bei analitinių sistemų, galinčių aptikti kelis komponentus, kūrimą. Taip pat svarbu užtikrinti validaciją lyginant su standartiniais metodais ir gerinti MIP sistemų konkurencingumą biologinių receptorių atžvilgiu.

Tyrimo metodika

Medžiagos ir cheminiai reagentai

Polimerų sintezei naudotas pirolas (98 %, „Alfa Aesar“, Vokietija), prieš naudojimą jis buvo distiliuotas. Geraniolis („Sigma-Aldrich“, JAV) ir acetonitrilas („Carl Roth GmbH & Co.“, Karlsruhe, Vokietija) naudoti be papildomo valymo. Kaip foninis elektrolitas naudotas ličio perchloratas ($LiClO_4$, „ThermoFisher“, Vokietija). Visi vandeniniai tirpalai ruošti naudojant itin gryną vandenį (0,055 µS/cm, 25 °C). Jutiklių valymui ir regeneracijai naudoti amonio hidroksidas (25 %, grynas, CAS No: 1336-21-6, Lenkija) ir vandenilio peroksidas (≥ 30 %, p. a., CAS No: 7722-84-1, Slovakija).

Įranga

Elektrocheminiai matavimai atlikti naudojant „Metrohm Autolab“ ir „Gamry“ potenciostatus. QCM eksperimentams naudotas 5 MHz aukso dengtas kvarco kristalas (QSX 301, „Biolin Scientific“) su srautinio tipo kamera. Masės pokyčiai ir adsorbcija stebėti realiuoju laiku.

Elektrocheminė sistema sudaryta iš trijų elektrodų: aukso darbinio elektrodo, Ag/AgCl etaloninio elektrodo ir platininio priešelektrodo. Taikyti metodai – CV ir EIS.

<u>Tirpalų paruošimas</u>

Tyrimuose naudota acetonitrilo ir vandens sistema su 0,1 mol/L $LiClO_4$. Pirolas ir geraniolis buvo tirpinami šioje terpėje skirtingoms funkcijoms.

Adsorbcijos tirpalai:

1AD – 0,1 mol/L $LiClO_4$ acetonitrile (naudotas kaip atraminis elektrolitas).

2AD – 0,005 mol/L geraniolio 1AD tirpale.

Polimerizacijos tirpalai:
1P – 0,05 mol/L pirolo 1AD tirpale.
2P – 0,05 mol/L pirolo ir 0,005 mol/L geraniolio 1AD tirpale.
Neutralus tirpalas:
A tirpalas – vandens ir acetonitrilo mišinys (50:50 tūrio santykiu), naudotas kaip bazinis (pradinis) tirpalas.
B1 tirpalas – 0,05 mol/L geraniolio A tirpale.
B2 tirpalas – 0,5 mol/L pirolo A tirpale.
KM eksperimentams naudotas 50:50 tūrio santykiu acetonitrilo ir vandens mišinys, užtikrinantis geraniolio tirpumą ir stabilų dažnio signalą.

Eksperimentinės sistemos

Tyrime naudotos dvi pagrindinės sistemos: elektrocheminė CV/EIS sistema ir KM masės stebėjimo sistema. Kiekviena jų buvo optimizuota atskirai, siekiant užtikrinti maksimalų matavimų stabilumą.

Skirtingos tirpiklių sistemos buvo taikomos pagal metodą: elektrocheminiams matavimams naudotas laidus $LiClO_4$ elektrolitas, o KM sistemai – mišrus tirpiklis, užtikrinantis stabilų rezonansinį signalą.

Visi eksperimentai atlikti bent du kartus, o esant didesniam nuokrypiui – papildomai pakartoti.

Aukso elektrodų paruošimas

Prieš kiekvieną eksperimentą aukso elektrodai buvo valomi elektrochemiškai, keičiant potencialą nuo –500 mV iki +1000 mV (Ag/AgCl). Procedūra kartota 3–10 kartų, kol gautas stabilus atsakas.

Adsorbcijos eksperimentai

Geraniolio adsorbcija ir polimero formavimas tirtas taikant CV, EIS ir KM metodus. Naudoti du eksperimentiniai režimai: trijų elektrodų elektrocheminė sistema ir KM sistema masės pokyčiams registruoti. EIS matavimai atlikti dažnių intervale nuo 10 kHz iki 2 Hz.

Geraniolio MIP formavimas

MIP plėvelės buvo formuojamos elektrocheminės polimerizacijos būdu ant aukso KM elektrodų. Paruoštos trys struktūros: vieno sluoksnio MIP, dvigubo sluoksnio MIP (NIP + MIP), NIP.

Polimerizacija atlikta CV metodu, kontroliuojant potencialą nuo –500 iki +850 mV. Dvigubo sluoksnio sistema pasižymėjo didesniu mechaniniu stabilumu ir geresniu struktūriniu vientisumu.

Analitės pašalinimas

Geraniolis iš MIP struktūrų pašalintas acetonitrilo ir vandens mišiniu (1:1), paskui elektrodai plauti ir džiovinti. Šis žingsnis užtikrino atvirų atpažinimo vietų formavimą.

KM aukso eleketrodų regeneracija

Aukso elektrodai regeneruoti naudojant piranijos tirpalą ($NH_4OH:H_2O_2$ = 60:40). Po valymo elektrodai buvo skalaujami vandeniu ir laikomi acetonitrilo ir vandens mišinyje.

AJM charakterizavimas

Paviršiaus morfologija tirta AJM *tapping* režimu. Tyrimo metu buvo analizuoti: švarus aukso paviršius, NIP sluoksnis ir MIP sluoksnis prieš analitės pašalinimą ir po jo. Naudojantis AJM metu gautais duomenimis vertinami šiurkštumo parametrai (R_q), paviršiaus homogeniškumas ir struktūriniai skirtumai.

Rezultatai ir aptarimas

Adsorbcijos ir sąveikos mechanizmai

Tyrimo rezultatai parodė, kad geraniolis ir pirolas pasižymi skirtingu adsorbciniu mechanizmu ant aukso ir polimero paviršiaus. Iš KM duomenų matyti, jog pirolas adsorbuojasi greitai ir efektyviai, sudarydamas pagrindą polimerizacijai, o geraniolis adsorbuojasi lėčiau, tačiau stabiliai išlieka susijungęs. Nors geraniolio koncentracija buvo mažesnė, jo adsorbcijos efektyvumas, perskaičiuotas remiantis koncentracija, buvo santykinai didelis, o tai rodo stiprią sąveiką su paviršiumi.

Nustatyta, kad vyksta konkurencinė adsorbcija tarp geraniolio ir pirolo. Geraniolis gali užimti aktyvias paviršiaus vietas ir taip riboti pirolo prieinamumą, kas tiesiogiai veikia polimerizacijos pradžią ir struktūros susidarymą. Tai patvirtina, kad adsorbcija yra esminis veiksnys, lemiantis MIP formavimosi mechanizmą.

Polimero formavimasis

Ciklinės voltamperometrijos (CV) rezultatai parodė, kad Ppy sluoksniai formuojasi etapais: pradinis kristalizacinių centrų susidarymas, augimas ir sluoksnio storėjimas. Vienasluoksnė MIP sistema pasižymėjo nestabiliu augimu dėl konkurencinės adsorbcijos, tuo tarpu dvisluoksnė sistema (su NIP pagrindu) užtikrino stabilesnį ir tolygesnį polimero formavimąsi.

NIP sluoksnis veikė kaip stabilizuojantis tarpinis sluoksnis, sumažinantis paviršiaus heterogeniškumą ir leidžiantis kontroliuoti tolesnį polimero augimą. Dėl to dvisluoksnė architektūra pasižymėjo geresniu struktūriniu vientisumu, tolygesniu sluoksnio pasiskirstymu ir didesniu atkartojamumu.

Kiekybinė adsorbcijos analizė

KM analizė parodė ryškius skirtumus tarp vienasluoksnės ir dvisluoksnės MIP sistemų. Dvisluoksnė sistema demonstravo kur kas didesnį dažnio pokytį (−34 Hz), atitinkantį apytikriai 602 ng adsorbuotos masės, o vienasluoksnė sistema rodė tik ~ 24 ng.

Apskaičiuota, kad dvisluoksnėje sistemoje susidaro labai didelis molekulių tankis (~ 10^{16} molekulių/cm^2), kas rodo ne tik paviršinę adsorbciją, bet ir molekulių difuziją į polimero vidų. Tai paaiškina matomą dalinį negrįžtamumą desorbcijos metu.

Kinetinė analizė

Kinetinė analizė parodė, kad adsorbcija vyksta pagal pseudo-antros eilės kinetiką, priklausančią tiek nuo difuzijos, tiek nuo aktyvių vietų prieinamumo. Desorbcija atitinka pirmos eilės kinetiką, būdingą kompleksų irimui.

Dvisluoksnė MIP sistema pasižymėjo didžiausiu adsorbcijos greičiu ir pusiausvyros konstanta, o tai rodo stipresnę ir efektyvesnę sąveiką su geranioliu. Tačiau kartu aptiktas ir ribotas desorbcijos efektyvumas, susijęs su molekulių įstrigimu polimero struktūroje ir heterogeninėmis prisijungimo vietomis.

Elektrocheminė sąsaja ir EIS analizė

EIS rezultatai parodė, kad geraniolio prisijungimas sukelia didelių sąsajos pokyčių. Įvyko dvigubo sluoksnio talpos sumažėjimas (ypač dvisluoksnėje sistemoje, ~ 2,5 karto), kas rodo sąsajos reorganizaciją ir dielektrinių savybių pokyčius.

Krūvio pernašos varža (R_{ct}) (angl. *charge transfer resistance*) dvisluoksnėje sistemoje išliko santykinai stabili, o tai rodo, kad polimero laidumas išlieka net ir vykstant adsorbcijai. Tai yra svarbu jutiklio funkcionalumui, nes leidžia išlaikyti signalą net esant stipriai sąveikai su analite.

Paviršiaus morfologija

AJM tyrimai parodė aiškius morfologinius pokyčius. NIP pasižymėjo didžiausiu šiurkštumu ir netvarkinga struktūra, vienasluoksnė MIP – lygesniu paviršiumi, o dvisluoksnė MIP – optimaliu balansu tarp struktūrinio vientisumo ir funkcinio heterogeniškumo.

Dvisluoksnėje sistemoje nustatyti gilesni ir labiau apibrėžti įdubimai, siejami su įspaustomis atpažinimo vietomis. Tai rodo efektyvesnį molekulinį įspaudimą ir didesnį aktyvių vietų prieinamumą.

Regeneracija ir stabilumas

Tyrimai parodė, kad visiška regeneracija nėra pasiekiama – po desorbcijos išlieka likutinis signalas. Tai susiję su stipria adsorbcija, difuziniais apribojimais ir heterogenine polimero struktūra. Dvisluoksnė sistema pasižymėjo geresniu stabilumu ir mažesniu signalo dreifu, tačiau negrįžtamumo problema išlieka kaip vienas pagrindinių šio tyrimo apribojimų.

Transiliacija

Tyrimo rezultatai rodo, kad sukurta geraniolio selektyvi MIP jutiklio sistema pasižymi aiškiu transiliaciniu potencialu, tačiau šiuo metu yra tarpinėje vystymosi stadijoje. Dvisluoksnė polimero architektūra (NIP + MIP) labai pagerino struktūrinį stabilumą, adsorbcijos efektyvumą ir elektrocheminio atsako atkuriamumą, o tai yra esminiai reikalavimai pereinant nuo laboratorinio prototipo prie praktinio taikymo.

KM, EIS ir AJM analizės nuosekliai parodė, kad jutiklio veikimas tiesiogiai priklauso nuo tarpfazinių adsorbcijos procesų ir polimero struktūros organizacijos. Šis mechanizmo išaiškinimas yra svarbus transiliaciniu požiūriu, nes leidžia kontroliuoti jutiklio savybes optimizuojant sintezę ir architektūrą. Tačiau nustatyta ir esminių apribojimų, ypač dalinis negrįžtamumas (nevisiška regeneracija), kuris gali riboti ilgalaikį jutiklio naudojimą ir pakartotinį pritaikymą.

Papildomi iššūkiai susiję su tuo, kad tyrimai atlikti esant santykinai didelėms analitės koncentracijoms ir paprastose sistemose, todėl jutiklio veikimas realiose, sudėtingose matricose (pvz., EA) dar nėra kaip reikiant įvertintas. Taip pat trūksta struktūriškai panašių junginių selektyvumo tyrimų, o tai yra kritinis aspektas praktiniam pritaikymui.

Iš technologinės pusės, elektropolimerizacija yra tinkama mastelio didinimui, tačiau, siekiant užtikrinti pakartojamumą tarp skirtingų jutiklių, reikia geresnės proceso kontrolės ir standartizacijos. Be to, būtina integruoti sistemą kartu su nešiojamąja elektronika, kad būtų galima pereiti prie realių, ne tik laboratorijos sąlygomis veikiančių prietaisų kūrimo.

Apibendrinant – dvisluoksnė MIP architektūra laikytina svarbiu žingsniu link praktiškai pritaikomų jutiklių kūrimo. Vis dėlto, siekiant visiškos transiliacijos, būtina spręsti regeneracijos, selektyvumo, darbo realiose matricose ir technologinės integracijos klausimus.

Išvados

1. Geraniolio adsorbcijos mechanizmas ant aukso elektrodų paviršių buvo sėkmingai ištirtas. Rezultatai parodė, kad geraniolis stipriai absorbuojasi ant elektrodo paviršiaus, o tai stipriai veikia vėlesnių polimerinių sluoksnių susidarymą ir jų tolygumą. Taigi, prieš kuriant MIP sistemas, yra svarbu suprasti analitės ir paviršiaus sąveiką.
2. MIP polipirolo sluoksniai buvo sukurti ir optimizuoti remiantis adsorbcijos mechanizmu. Dviejų sluoksnių sistema, susidedanti iš NIP pagrindo sluoksnio ir virš jo formuojamo įspausto sluoksnio, padidino polimerizacijos stabilumą ir užtikrino labiau kontroliuojamą atpažinimo vietų formavimąsi net esant santykinai didelėms geraniolio koncentracijoms.
3. Polimerinių sluoksnių morfologija ir struktūrinės savybės buvo analizuotos naudojant atominės jėgos mikroskopiją (AJM). Šie tyrimai patvirtino ištisinių ir tolygių polimerinių sluoksnių susidarymą bei suteikė informacijos apie sluoksnių storį ir paviršiaus topografiją. Nors atskirų molekulinių ertmių tiesiogiai vizualizuoti nebuvo įmanoma, gauti duomenys patvirtina struktūruotų polimerinių plėvelių susidarymą, kurį lemia analitės adsorbcija.
4. Tyrimo metu buvo įvertintas sukurtos sistemos, kaip elektrocheminio jutiklio prototipo, pritaikomumas. Tyrimas parodė, kad suformuota MIP sistema geba reaguoti į geraniolį ir sudaro pagrindą tolesnei optimizacijai. Taip pat pabrėžiamos galimybės šią laboratorinę jutiklio sistemą pritaikyti praktiniuose analitiniuose tyrimuose arba įrenginiuose.

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