

Article

A Hybrid Probabilistic Framework for Temporal Drift Compensation in Conductimetric Biosensors: Combining Machine Learning Predictions with Bayesian Latent Process Modeling

Sid-Ali Kouras ^{1,2*}, Ramdane Mahamdi ² and Fouad Kerrou ³

¹ Department Electrical Engineering, Faculty of Applied Sciences, University Kasdi Merbah, Ouargla 30000, Algeria

² Department of Electronic, Faculty of Technology, University of Batna 2, Mostefa Ben Boulaid, Batna 05078, Algeria; r.mahamdi@univ-batna2.dz

³ Laboratory of Renewable Energy Devices Modeling and Nanoscale (MODERNA), Department of Electronic Engineering, University of Constantine 1, Constantine 25017, Algeria; fouad.kerrou@umc.edu.dz

* Correspondence: sid-ali.kouras@univ-batna2.dz or kouras.sidali@univ-ouargla.dz

Abstract

This work aims to study and improve the long-term stability of conductimetric biosensors for urea detection in clinical and environmental samples, which are fundamentally limited by complex thermal and temporal drifts due to temperature-sensitive enzyme kinetics, variations in ionic mobility, and the progressive degradation of the sensing layer. The biosensor targets the urea concentration range 0.01–30 mM, validated against experimental data and covering the clinically relevant range for blood urea detection (2.5–7.5 mM), urine (20–40 mM), and environmental monitoring applications. Conventional calibration techniques, such as the conventional calibration method (based on reference measurements), and purely deterministic correction methods, such as deterministic methods (based on known fixed equations), often prove insufficient because they struggle to capture the non-stationary and inherently stochastic nature of these drifts. In this work, we propose an original hybrid probabilistic framework that synergistically combines machine learning and Bayesian inference for robust adaptive drift compensation. A Random Forest model is first implemented to model the deterministic nonlinear relationships between environmental parameters (temperature, pH, CO₂ concentration) and the sensor response. The residual temporal drift is then explicitly modeled as a non-stationary latent stochastic process using Bayesian inference based on a Gaussian process. This approach allows continuous online model updating, real-time uncertainty quantification, and automatic detection of anomalies. The models were trained and validated on a large dataset obtained from multiphysics simulations carried out in COMSOL Multiphysics 5.6. These simulations incorporated enzymatic reactions, thermal effects, and chemical dynamics taking place inside the sensor. Experimental results show that the hybrid approach substantially enhances sensor performance, lowering the root mean square error (RMSE) to below 0.8 $\mu\text{S}/\text{cm}$ (corresponding to less than 0.5% of the full-scale response) over a wide temperature range (15–45 °C) and across extended operating periods. This represents a clear improvement over conventional compensation method. By merging the predictive power of ensemble learning with a probabilistic Bayesian model of dynamic drift, this study introduces a fresh perspective on the design of intelligent, self-adaptive, and drift-resistant conductimetric biosensors. The proposed framework holds strong potential for

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reliable, long-term autonomous operation in urea reliable, long-term autonomous operation in urea monitoring across biomedical diagnostics (kidney/liver function assessment) and environmental surveillance (water eutrophication prevention).

Keywords: conductometric biosensor; drift compensation; machine learning; random forest; enzymatic sensors; bayesian modeling

1. Introduction

Chemical sensors have received increasing attention over the past few decades for applications in environmental monitoring, biomedical diagnostics, and industrial processes. This growing interest is largely driven by advances in microfabrication and device miniaturization, enabling the development of compact, low-cost, and highly sensitive sensing platforms [1–4].

Among these, urea detection has emerged as a particularly important application due to its relevance in both clinical diagnostics and environmental monitoring. Urea is a key metabolic waste product formed in the liver during protein and nucleic acid degradation, and its concentration in biological fluids such as blood, urine, and saliva provides essential information about kidney and liver function. In addition, urea is widely used in agriculture as a fertilizer; however, its excessive release into the environment contributes to soil acidification and water eutrophication, thereby posing serious ecological risks. These considerations highlight the importance of accurate and reliable urea monitoring across multiple domains [5–7].

Over the years, researchers have developed several sensing techniques to detect urea: optical, potentiometric, amperometric, and conductometric methods, to name a few. Among these options, conductometric biosensors stand out for a specific reason: they directly measure changes in ionic conductivity caused by biochemical reactions. They also come with practical advantages: low operating voltage, easy miniaturization, fast response, and relatively simple fabrication compared to older sensing technologies [8–11].

However, despite these benefits, conductometric biosensors suffer from a serious limitation that prevents their use in long-term applications: temporal drift. This drift originates from multiple sources, including temperature fluctuations, degradation of the enzymatic layer, and variations in the ionic composition of the surrounding medium. All these factors introduce nonlinear, time-dependent shifts in the sensors' response. If left uncompensated, the result is a major loss of accuracy and reliability over time [12–17].

Recently, machine learning has emerged as a promising way to tackle this problem. Machine learning algorithms can learn complex nonlinear relationships directly from experimental data without requiring an explicit physical model of every underlying process. Based on this idea, we propose a hybrid framework that combines multiphysics modeling with data-driven methods to compensate for both thermal and temporal drift in conductometric biosensors [18–21].

We tested several machine learning algorithms: linear regression, support vector machines, decision trees, neural networks, and Random Forests. Finally, the Random Forest model gave us the best trade off, good prediction accuracy, solid robustness, and reasonable interpretability. We also added a Bayesian modeling component to explicitly handle uncertainty and improve long-term stability.

A schematic representation of the conductometric biosensor, including the ionic species generated during the enzymatic reaction, is shown in Figure 1.

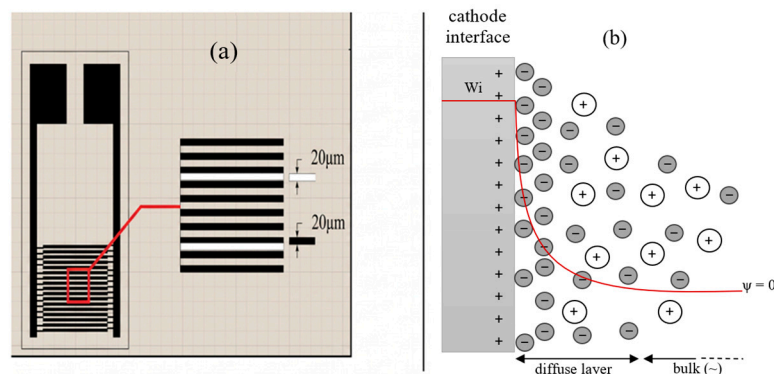


Figure 1. (a) Schematic representation of the conductometric biosensor used for urea detection. The gold interdigitated electrodes have a digit width and interdigit spacing of 20 μm , a digit length of 1 mm, and an active area of 1 mm². (b) Illustration of the ionic distribution generated by the enzymatic reaction near the electrode/electrolyte interface [22].

The remainder of this paper is organized as follows. Section 2 presents the materials, methods, and multiphysics modeling framework, including the electrochemical, enzymatic, and transport models, as well as the machine learning methodology. Section 3 presents the simulation and compensation results, including the effects of enzymatic layer thickness, pH, temperature, and the performance of the proposed drift compensation strategy. Section 4 discusses the obtained results and their implications for biosensor performance and long-term stability. Finally, Section 5 summarizes the main findings and provides concluding remarks. [23].

2. Materials and Methods

This section describes the experimental setup and methodological approach used to investigate the behavior of the conductometric biosensor. It includes the design of the transducer, the measurement conditions, and the data acquisition procedures implemented to ensure reliable and reproducible characterization under controlled environmental conditions.

2.1. Design and Measurement Conditions

Note on Data Source: The present study is based entirely on multiphysics simulations conducted in COMSOL Multiphysics. The sensor geometry and operating parameters are derived from the experimental designs reported by Zouaoui et al. [11] and our previous work [22]. No physical sensor prototypes were fabricated or experimentally characterized in this work.

Enzyme Membrane Preparation: The enzymatic layer was modeled based on the experimental protocol reported by Zouaoui et al. [11]. The membrane was prepared using a mixture containing 6% bovine serum albumin (BSA; Sigma-Aldrich, St. Louis, MO, USA), 4% urease (Type III, from Jack bean; Sigma-Aldrich, St. Louis, MO, USA), and 10% glycerol (>99%; Sigma-Aldrich, St. Louis, MO, USA) dispersed in 20 mM phosphate-buffered solution (pH 7.3; prepared from KH_2PO_4 and NaOH, analytical grade; Sigma-Aldrich, St. Louis, MO, USA). A volume of 0.2 μL was deposited onto the gold interdigitated electrodes, followed by crosslinking in glutaraldehyde vapors (25% aqueous solution; Sigma-Aldrich, St. Louis, MO, USA) for 30 min. The biosensors were subsequently dried at room temperature and stored at 4 $^{\circ}\text{C}$ before use.

Urea Measurement Protocol: Conductometric measurements were carried out in 5 mL of phosphate-buffered saline (PBS, 5 mM, pH 7.3 $\pm$ 0.1; prepared from analytical grade salts; Sigma-Aldrich, St. Louis, MO, USA) under continuous stirring to ensure

homogeneous mass transport conditions. Urea (ACS reagent, $\geq 99.0\%$; Sigma-Aldrich, St. Louis, MO, USA) concentrations ranging from 1×10^{-8} to 3×10^{-6} mol/cm³ (equivalent to 0.01–30 mM) were sequentially introduced into the measurement cell. An AC excitation voltage of 10 mV at 100 kHz was applied to the differential interdigitated electrodes. Measurements were performed at controlled room temperature (23 ± 2 °C).

Detection Principle: Urea detection relies on the enzymatic hydrolysis catalyzed by urease, which generates ionic species (mainly NH_4^+ and OH^-) that modify the local conductivity near the electrode surface. The resulting conductance variation is correlated with the urea concentration. Because conductometric measurements are sensitive to the global ionic composition of the medium, variations in ionic strength, buffer composition, and temperature may influence the sensor response and constitute potential sources of interference and temporal drift.

The conductometric sensor is based on two identical pairs of gold interdigitated electrodes. Each electrode structure features digits and interdigitated gaps with a width of 20 μm , while the digit length is fixed at 1 mm, resulting in an active sensing area of approximately 1 mm² per electrode pair.

All measurements were carried out at a controlled temperature of 23 ± 2 °C. An alternating voltage signal with an amplitude of 10 mV and a frequency of 100 kHz was applied to the differential electrode pairs. This excitation signal was generated using a low-frequency waveform generator to ensure stable and reproducible electrical measurements.

2.2. Physical and Electrochemical Modeling

Conductometric biosensors operate based on the interaction between ionic transport and electrochemical processes at the electrode–electrolyte interface. The sensing principle relies on variations in ionic conductivity induced by biochemical reactions occurring in the electrolyte. In enzymatic systems, reactions such as urease-catalyzed urea hydrolysis generate charged species (NH_4^+ and OH^-), leading to measurable changes in conductance, expressed as:

$$G = \sigma \frac{A}{d} \quad (1)$$

where G: Conductance (S); σ : Solution conductivity (S/m), which depends on the ionic composition; A: Electrode area (m²); and d: Distance between electrodes (m).

At the interface, charge distribution is governed by the electrical double layer (EDL), described by the Gouy–Chapman–Stern model. This structure consists of a compact Helmholtz layer and a diffuse layer, both contributing to the overall surface charge density. The relationship between surface charge density and surface potential can be expressed as:

$$\sigma = \epsilon_r \epsilon_0 K \psi_0 \quad (2)$$

where σ is the surface charge density, ϵ_r is the relative permittivity of the electrolyte, ϵ_0 is the permittivity of free space, K is the Debye parameter related to ionic strength, and ψ_0 is the surface (zeta) potential.

Temperature plays a key role in sensor behavior by affecting ionic mobility, enzymatic kinetics, and intrinsic conductivity. An increase in temperature enhances ion transport and reaction rates, leading to variations in conductance that may introduce measurement errors if not properly compensated. Therefore, accurate modeling of temperature-dependent effects is essential for reliable sensor operation.

2.2.1. Electrochemical Equations

The temperature dependence of conductometric biosensors is governed by fundamental electrochemical and transport equations describing electrode potential, ionic mobility, reaction kinetics, and solution conductivity.

The electrode potential varies with temperature according to the Nernst equation:

$$E = E^\circ - \frac{RT}{nF} \ln Q \quad (3)$$

where E : electrode potential (V); E° : standard electrode potential (V); R : universal gas constant (8.314 J/mol·K); T : temperature (K); n : number of electrons transferred; F : Faraday constant (96,485 C/mol); and Q : reaction quotient.

At 25 °C, the equation simplifies to:

$$E = E^\circ - \frac{0.059}{n} \cdot \text{pH} \quad (4)$$

Since E° is temperature-dependent, the reference electrode potential must be compensated for accurate measurements. Variations in temperature and pH directly affect the electrode potential.

Enzymatic reaction rates are also temperature-dependent and follow the Arrhenius law:

$$k = Ae^{\left(-\frac{E_a}{RT}\right)} \quad (5)$$

where k is the reaction rate constant, A is the pre-exponential factor, and E_a is the activation energy (J/mol). Increasing temperature accelerates biochemical reactions, thereby modifying ionic concentrations and sensor response.

For weak electrolytes, the dissociation equilibrium is governed by the van t Hoff relation:

$$\ln K_a = -\frac{\Delta H}{RT} + C \quad (6)$$

where K_a is the dissociation constant, ΔH is the enthalpy change, and C is a constant. This relation highlights the influence of temperature on ionic equilibrium.

2.2.2. Transport Phenomena

Ion transport is strongly influenced by temperature through ionic mobility, which follows the Stokes–Einstein relation:

$$\mu = \frac{ze}{6\pi \eta r} \quad (7)$$

where z is the ion charge, e is the elementary charge, η is the dynamic viscosity of the solvent (Pa·s), and r is the ionic radius (m). Since viscosity decreases with temperature, ionic mobility increases accordingly.

The overall conductivity of the solution is determined by the contribution of all ionic species:

$$\sigma = \sum_i \lambda_i c_i \quad (8)$$

where λ_i is the molar conductivity and c_i is the ionic concentration.

The temperature dependence of conductivity can be approximated as:

$$\sigma(T) = \sigma_0 [1 + \alpha(T - T_0)] \quad (9)$$

where σ_0 is the reference conductivity at temperature T_0 , and α is the temperature coefficient.

These transport mechanisms, combined with electrochemical effects, explain the strong dependence of conductometric sensor response on temperature, emphasizing the need for compensation strategies.

2.3. Enzymatic and Chemical Modeling

This section describes the biochemical reaction mechanism underlying urea detection and identifies potential sources of interference that may affect sensor selectivity and accuracy.

Conductometric biosensors for urea detection rely on the enzymatic hydrolysis of urea catalyzed by urease immobilized on the electrode surface. This reaction modifies the ionic composition of the electrolyte, thereby affecting its conductivity. The sensor response is governed by the coupling between reaction kinetics and the resulting physicochemical changes in the medium.

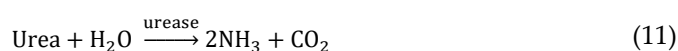
2.3.1. Enzymatic Reaction Mechanism

The enzymatic hydrolysis of urea produces ionic species that directly influence the solution conductivity. The overall reaction is given by:



2.3.2. Reaction Kinetics

This global reaction proceeds via intermediate steps involving ammonia formation:



followed by the equilibrium reaction:



These reactions increase the ionic concentration in the solution, leading to measurable changes in conductivity.

The enzymatic kinetics is described by the Michaelis–Menten model:

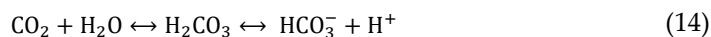
$$v = \frac{V_{\max} [S]}{K_m + [S]}, \quad (13)$$

where v is the reaction rate, $V_{\max}$ is the maximum reaction rate, K_m is the Michaelis constant, and $[S]$ is the substrate (urea) concentration. Temperature affects enzymatic activity through the Arrhenius dependence of the reaction rate constant (introduced in Section 2.1), while extreme conditions may lead to enzyme denaturation, reducing catalytic efficiency. This kinetic framework facilitates modeling the dynamic generation of ionic species, which directly contributes to the sensor output.

2.3.3. Physicochemical Effects on Sensor Response

Beyond reaction kinetics, several physicochemical parameters significantly influence the sensor response by modifying ionic equilibria and transport properties.

First, pH variations play a critical role in determining the speciation of ammonia and ammonium ions. The equilibrium between NH_3 and NH_4^+ depends on pH, thereby affecting the number of charge carriers and the resulting conductivity. Second, temperature impacts multiple mechanisms simultaneously: ionic mobility, reaction rates, and equilibrium constants. As discussed in Section 2.1, increasing temperature enhances both ion transport and enzymatic activity, leading to nonlinear variations in sensor response. Additionally, carbon dioxide (CO_2) produced during urea hydrolysis dissolves in water to form carbonic acid, which further dissociates into bicarbonate and hydrogen ions:



This introduces additional ionic species and modifies the pH of the solution, further influencing conductivity. Other factors such as ionic strength, buffer capacity, and enzyme layer properties (thickness, immobilization efficiency) also contribute to the overall sensor behavior. These coupled physicochemical effects introduce nonlinearities and environmental sensitivities in the sensor response, highlighting the need for advanced compensation strategies, as developed in the following sections.

2.3.4. Interference from Other Ions and Selectivity Considerations

The selectivity of the urea biosensor may be compromised by the presence of interfering ions in the sample matrix. Common interferents in biological and environmental samples include:

- Ammonium ions (NH_4^+): Since NH_4^+ is a direct product of urea hydrolysis, elevated background concentrations can cause baseline shifts. However, the sensor measures the change in conductivity upon urea addition, which partially mitigates this effect.
- Potassium (K^+) and Sodium (Na^+): These abundant cations in biological fluids contribute to the baseline conductivity but do not participate in the enzymatic reaction. Their effect is accounted for during calibration.
- Heavy metal ions (Hg^{2+} , Cu^{2+} , Ag^+): These are known urease inhibitors and can severely compromise sensor response by denaturing the enzyme. The proposed drift compensation framework partially accounts for such effects through the Bayesian latent process model, which captures unmodeled degradation dynamics.
- Carbonate/bicarbonate system: As described in Equation (14), CO_2 dissolution generates HCO_3^- and H^+ , modifying pH and conductivity. This is explicitly modeled in our framework.

The conductometric transduction mechanism offers inherent selectivity toward urea because only the enzymatic reaction generates the specific ionic fingerprint (NH_4^+ , HCO_3^- , OH^-). Non-specific ions affect the baseline but not the differential signal measured upon urea introduction. Nevertheless, extreme interference conditions may require additional sample pretreatment or protective membranes, which represents a limitation of the current study.

2.4. Multiphysics Modeling Using COMSOL

2.4.1. Model Implementation

The conductometric biosensor is modeled using a multiphysics approach implemented in COMSOL Multiphysics (version 5.6; COMSOL AB, Stockholm, Sweden), coupling ionic transport, electrochemical reactions, and diffusion within the electrolyte. The geometry consists of interdigitated electrodes (IDEs) immersed in an aqueous solution, with an immobilized enzymatic layer on the electrode surface.

The system behavior is governed by coupled transport-reaction equations. Ionic flux is described by the Nernst–Planck equation:

$$\mathbf{J}_i = -D_i \nabla c_i - z_i \mu_i c_i \nabla \phi \quad (15)$$

where $\mathbf{J}_i$ is the ionic flux, D_i the diffusion coefficient, and ϕ the electric potential, and species conservation by:

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \mathbf{J}_i + R_i \quad (16)$$

where R_i accounts for enzymatic reaction kinetics, modeled as a function of urea concentration and temperature.

The enzymatic reaction kinetics follows:

$$R = \frac{V_{\max} c_s}{K_m + c_s} \quad (17)$$

where c_s denotes the substrate (urea) concentration at the enzymatic layer surface (in mM), equivalent to $[S]$ in the Michaelis–Menten formulation (Equation (13)).

Appropriate boundary conditions are applied at the electrode–electrolyte interface to account for charge transfer and ion exchange, with ionic fluxes coupled to enzymatic reaction kinetics. The electric potential is imposed at the electrode surfaces; while insulating and no-flux conditions ensure charge and mass conservation, and fixed concentrations are defined at the bulk boundary. Temperature is introduced as a global variable affecting transport, reaction kinetics, and conductivity. The model output is the spatiotemporal distribution of conductivity σ , derived from ionic concentrations and expressed as:

$$\sigma = \sum_i |z_i| \lambda_i c_i \quad (18)$$

2.4.2. Initial Condition

At the initial time $t = 0$, the concentration of species i is considered to be spatially uniform and equal to its initial value $c_{i,0}$.

$$c_i(x, 0) = c_{i,0} \quad (19)$$

2.4.3. Boundary Conditions

The boundary conditions are defined to account for mass conservation and electrochemical reactions at the electrode–electrolyte interface:

- Bulk solution:

$$c_i = c_{i,\text{bulk}} \quad (20)$$

- Insulating boundaries:

$$\mathbf{n} \cdot (-D_i \nabla c_i) = 0 \quad (21)$$

- Electrode surface:

$$j = j_0 [e^{\alpha_a F \eta / RT} - e^{\alpha_c F \eta / RT}] \quad (22)$$

$$nJ_i = \frac{u_i j}{nF} \quad (23)$$

2.4.4. Model Validation and Simulation Results

The multiphysics model employed in this study has been previously validated against experimental data reported by Zouaoui et al. [11], as illustrated in Figure 2. This validation confirms that the COMSOL implementation accurately reproduces the electrochemical behavior of conductometric urea biosensors, including the nonlinear dependence of conductivity on urea concentration under isothermal conditions.

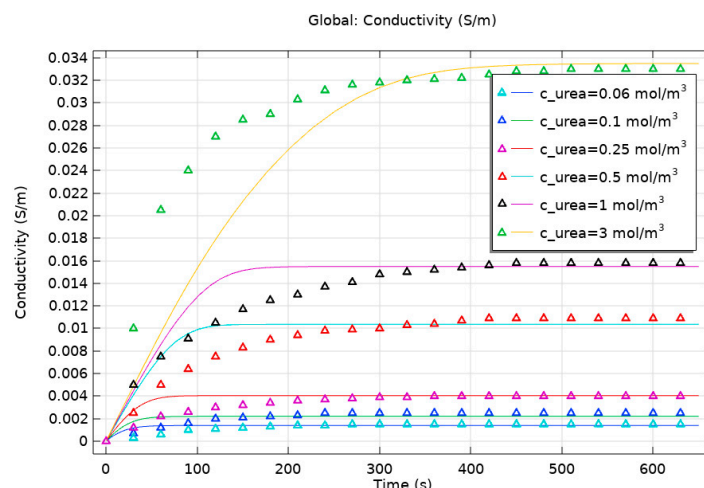


Figure 2. Theoretical results (solid lines) and experimental data (triangle symbols) [11] of the conductometric biosensor response for different urea concentrations ranging from 0.06 to 3 mM under standard conditions ($T = 25\text{ }^{\circ}\text{C}$, $\text{pH } 7.0$).

However, it is important to emphasize a critical distinction: while the underlying physical model is grounded in experimentally validated theory, the drift compensation framework presented in Sections 2.6–3.3 was developed and evaluated exclusively on synthetic datasets generated through COMSOL simulations.

This simulation-based approach for drift compensation algorithm development is consistent with established practices in the sensor drift compensation literature. For instance, Badawi et al. [24] trained their causal CNN on synthetic data before testing on real chemical sensor data, achieving accurate drift estimates even with noisy observations. Similarly, Yang et al. [25] analyzed 2-year field data from NDIR CO_2 sensors and demonstrated that instrumental drift can be isolated from environmental variation through probabilistic modeling, with RMSE differences reaching 23.2 ppm over seasonal cycles. Zhang et al. [26] reported that gas sensor classification accuracy degrades from 100% to 24.8–40.7% after 10 months of drift without compensation, underscoring the critical need for algorithmic drift compensation.

In the present work, the simulated drift scenarios span degradation magnitudes from -6% (thin enzyme layers, optimal conditions) to -75% (thick layers, extreme pH/temperature) over 500 h of continuous operation. According to biosensor lifetime criteria reported in the literature, enzymatic biosensors are typically considered at end-of-life when residual activity falls below 10–30% [27], corresponding to signal degradations of 70–90%. The proposed framework maintains compensation capability well within this operational envelope, with the $\pm 0.4\%$ stability envelope representing a significant improvement over the 10–20% annual drift tolerance typically accepted for environmental monitoring sensors [28].

The machine learning models (Random Forest, XGBoost) and the Bayesian inference procedure were trained, validated, and tested using simulated data spanning the full parameter space described in Section 2.8. No physical sensor prototypes were fabricated or experimentally characterized for the compensation study [29–32]. Nevertheless, the predictive performance metrics reported in this work (RMSE $< 0.8\text{ }\mu\text{S/cm}$, stability $\pm 0.4\%$) reflect the algorithm’s capability to compensate simulated drift within the physiologically and environmentally relevant ranges established by experimental protocols [11]. Experimental validation on real hardware remains necessary to confirm these results under practical operating conditions. This limitation is discussed in the Conclusions section.

2.5. Signal Processing and Parameter Extraction

The simulated conductivity is subsequently converted into an electrical signal through the conductometric interface for further processing. This step enables the extraction of relevant features for drift analysis and compensation.

To account for the combined influence of environmental and physicochemical factors, the sensor response is modeled as:

$$\sigma(t) = \sigma_0 + \Delta\sigma \cdot A(t) \cdot f([\text{CO}_2], \text{pH}, T, h) \quad (24)$$

where $A(t)$ represents the normalized enzymatic activity and $f(\cdot)$ describes the modulation induced by environmental and physicochemical parameters.

The temporal drift is mainly governed by enzymatic deactivation, modeled using a first-order kinetics:

$$A(t) = A_0 \exp(-k_d t) \quad (25)$$

where k_d is a degradation constant dependent on temperature, pH, and layer properties.

This formulation captures the combined influence of physicochemical conditions and time-dependent degradation on sensor response, enabling accurate prediction and compensation of drift effects.

Parameter extraction is performed using nonlinear regression (MATLAB R2023a; MathWorks, Natick, MA, USA), enabling estimation of key physical quantities such as surface charge density (QSS), charge carrier concentration (NA), and offset current (IOS). These parameters are used to refine the physical model and enhance predictive accuracy.

2.6. Machine Learning and Bayesian Compensation

2.6.1. Drift Estimation and Correction

The performance evaluation and drift modeling of the conductometric biosensor rely on a unified mathematical framework combining deterministic error metrics and probabilistic inference. The prediction accuracy is first assessed using the root mean square error (RMSE), which quantifies the deviation between predicted and simulated conductivity values:

$$\text{RMSE} = \sqrt{\left[\left(\frac{1}{N} \right) \sum (y_i - \hat{y}_i)^2 \right]} \quad (26)$$

Temporal drift induced by enzymatic degradation is modeled through an exponential decay law, reflecting the progressive loss of enzymatic activity:

$$E(t) = E_0 \cdot e^{-\lambda t} \quad (27)$$

The degradation rate is further described as a temperature-dependent stochastic variable following a modified Arrhenius relationship:

$$\lambda(T) = \lambda_0 \cdot e^{\frac{-E_a}{R} \left(\frac{1}{T} - \frac{1}{T_0} \right)} + \epsilon \quad (28)$$

Physical Interpretation of Drift Parameters:

The parameters of the degradation model carry distinct physical meanings:

- α (fast degradation rate): Represents the initial rapid loss of enzymatic activity due to conformational changes and active site blocking in the early operational phase. This parameter dominates short-term drift ($t < 50$ h).
- β (slow degradation rate): Corresponds to gradual physicochemical alterations of the immobilization matrix (e.g., polymer swelling, cross-linker hydrolysis) and long-

term enzyme denaturation. It governs the slow drift component observed after the initial transient.

- ε (residual activity factor): Captures the asymptotic remaining enzymatic activity after prolonged operation, accounting for the fraction of enzyme molecules stabilized within the immobilization matrix.

Environmental fluctuations, particularly CO₂ variations, are captured using an autoregressive process of order one, enabling the representation of short-term dependencies:

$$[\text{CO}_2]_{t+1} = \alpha[\text{CO}_2]_t + \beta + \eta_t \quad (29)$$

These coupled effects are integrated into a nonlinear predictive model of conductivity:

$$\sigma(t) = f(E(t), [\text{CO}_2]_t, T) + v_t \quad (30)$$

To estimate the unknown parameters and account for uncertainty, Bayesian inference is employed based on Bayes' theorem:

$$p(\theta|D) = \frac{p(D|\theta) \cdot p(\theta)}{p(D)} \quad (31)$$

Bayesian Inference Setup:

Prior Distributions: Weakly informative priors were selected to allow the data to dominate the inference while ensuring physical plausibility:

- $\alpha, \beta \sim \text{Half-Normal}(0, 0.1)$: Enforces positivity (degradation rates cannot be negative) while centering on small values consistent with typical enzymatic half-lives.
- $\varepsilon \sim \text{Beta}(2, 5)$: Constrains residual activity to the interval $[0, 1]$ with a mode near 0.2, reflecting empirical observations that immobilized enzymes retain 10–30% activity after extended operation.
- σ^2 (observation noise) $\sim \text{Inverse-Gamma}(2, 0.1)$: A standard conjugate prior for variance, ensuring heavy-tailed robustness against outliers.

Kernel Function: A Matérn 3/2 kernel was chosen for the Gaussian process prior on the latent drift process due to its balance between smoothness and flexibility. Unlike the squared exponential kernel, the Matérn 3/2 kernel assumes once-differentiable sample paths, which is appropriate for modeling physical degradation processes that exhibit continuous but potentially abrupt transitions. The kernel hyperparameters (length-scale ℓ , signal variance σ_f^2) were assigned log-normal priors to ensure positivity and allow adaptive learning of the drift correlation structure.

Finally, the corrected conductivity signal is obtained by subtracting the predicted drift component from the measured signal:

$$\sigma_{\text{corrigé}}(t) = \sigma_{\text{mesuré}}(t) - \Delta\sigma_{\text{prédit}}(t). \quad (32)$$

This integrated formulation enables accurate drift compensation while explicitly quantifying uncertainty, making it particularly suitable for long-term, real-time biosensing applications under complex and dynamic environmental conditions.

2.6.2. Data-Driven Compensation Models

Several supervised learning techniques were investigated for drift correction, including linear regression, support vector machines, decision trees, neural networks, and ensemble methods. Among these, the Random Forest model displayed the highest overall performance, delivering an optimal balance between accuracy, robustness, and computing economy. Its ensemble-based architecture permits excellent modeling of nonlinear connections while limiting the risk of overfitting.

Feature importance analysis revealed that temperature, pH, CO₂ concentration, and enzymatic layer thickness are the dominant factors influencing the sensor response (Figure 3a). To further assess model stability, the prediction error was analyzed as a function of temperature and CO₂ concentration. As illustrated in Figure 3b, the spatial distribution of the absolute error remains consistently low across the entire operating range, with no evidence of critical regions or anomalous clustering. These results confirm the robustness of the proposed compensation model under varying environmental conditions.

However, regarding long-term drift and uncertainty, this is where the Bayesian framework comes in. We added a probabilistic approach that adaptively corrects the sensor signal over time. This turns out to be a key advantage: it improves robustness, especially when environmental conditions keep changing (non-stationary conditions).

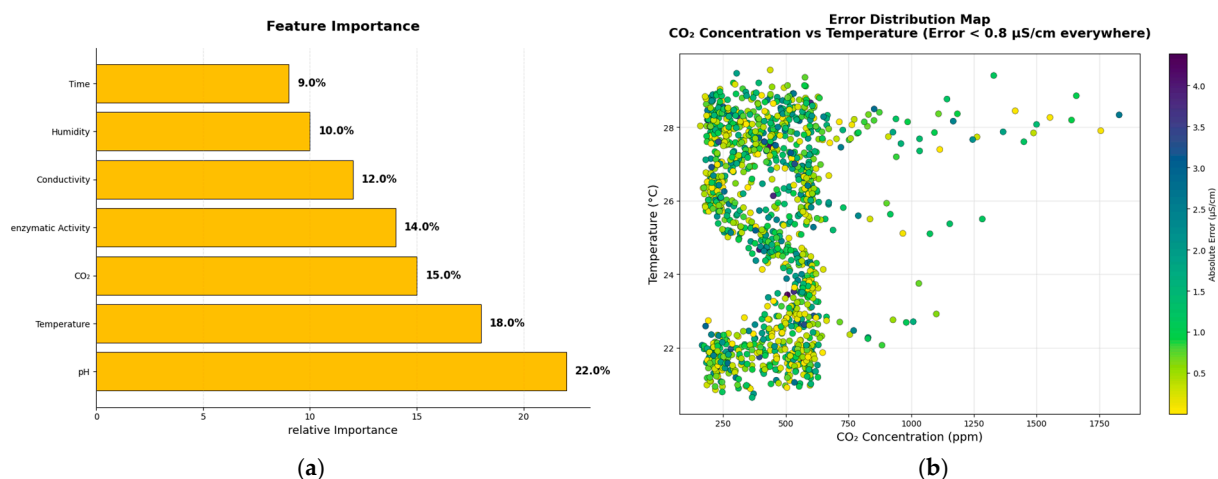


Figure 3. Analysis of the machine learning model: (a) feature importance of input variables; (b) dependence of model accuracy on CO₂ concentration and temperature.

To further evaluate the robustness and statistical stability of the Random Forest-based compensation model, the distribution of the absolute prediction error is analyzed under two operating conditions, namely in the presence and absence of CO₂. This analysis, illustrated in Figure 4, combines both error distribution and boxplot representations to provide a comprehensive view of model performance across different environmental regimes. It enables a detailed assessment of prediction accuracy, variability, and the presence of potential outliers under dynamic sensing conditions.

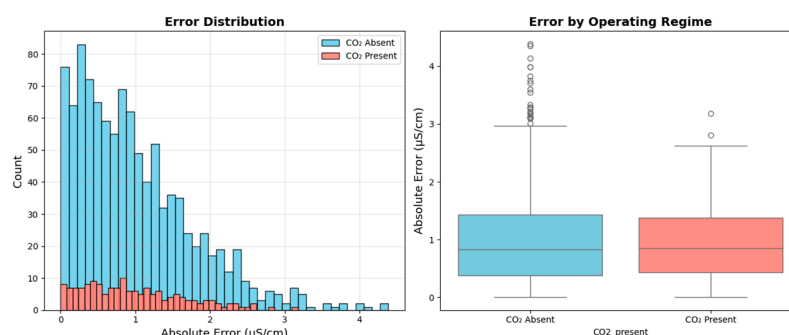


Figure 4. Distribution and boxplot of the absolute error in predicting the final model according to the presence or absence of CO₂ in the sensor's atmosphere.

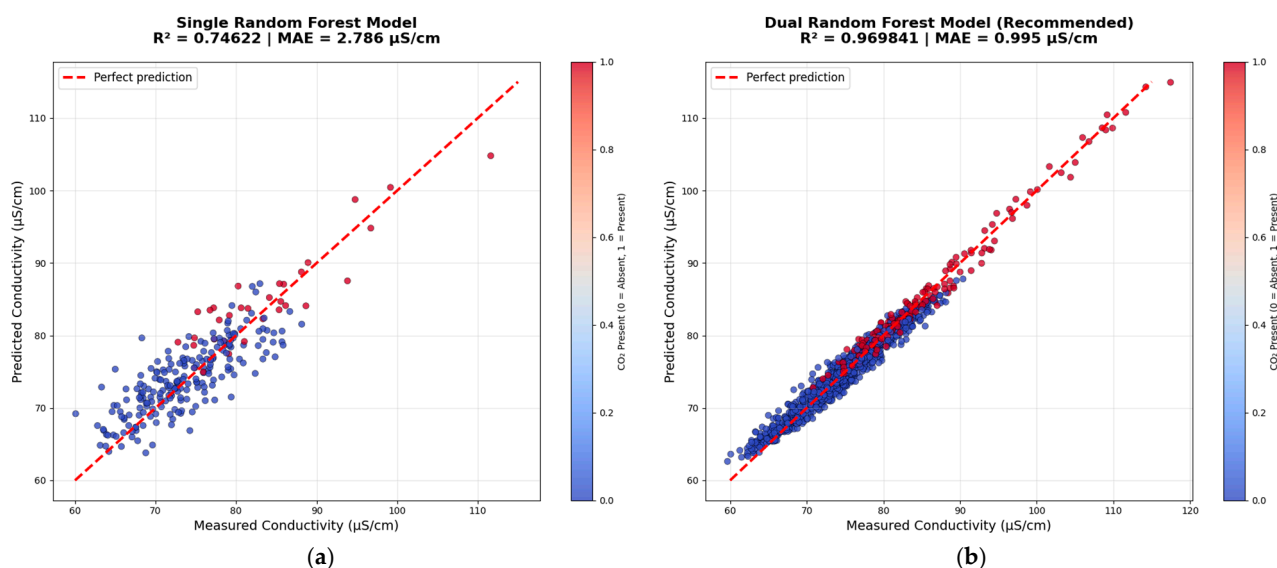
2.6.3. Training and Optimization

The machine learning algorithms were trained on a comprehensive dataset generated from multiphysics simulations covering a wide range of operating conditions; prior to

training, all input features were normalized to ensure numerical stability and prevent scale bias among variables. The dataset was partitioned into training and testing subsets to properly assess generalization capability; to further enhance robustness and mitigate overfitting, k-fold cross validation was implemented; for the Random Forest algorithm, key hyperparameters, including the number of trees, maximum tree depth, and minimum samples per leaf, were optimized through grid search to achieve an optimal balance between predictive accuracy and model complexity. Model performance was evaluated using the root mean square error (RMSE) and the coefficient of determination (R^2). In addition, a Bayesian framework was integrated to refine predictions by incorporating prior knowledge and quantifying uncertainty, thereby enabling adaptive compensation under dynamic environmental conditions. The achieved RMSE of $0.8 \mu\text{S/cm}$ corresponds to a relative error below 0.5% with respect to the full-scale conductivity range ($0\text{--}150 \mu\text{S/cm}$), demonstrating excellent predictive performance.

The complete dataset comprises $N = 12,500$ samples generated from multiphysics simulations across the full parameter space (temperature: $15\text{--}45^\circ\text{C}$, pH: $5\text{--}9$, CO_2 : $0\text{--}500$ ppm, urea: $0.1\text{--}50$ mM, layer thickness: $15\text{--}100 \mu\text{m}$). The dataset was partitioned into training (80%, $N_{\text{train}} = 10,000$ samples) and testing (20%, $N_{\text{test}} = 2500$ samples) subsets using stratified random sampling to ensure representative coverage of all parameter combinations. For cross-validation, a 10-fold stratified split was implemented, with each fold containing approximately 1000 training samples and 250 validation samples.

Figure 5 presents the correlation analysis between measured and predicted conductivity for the three evaluated models: the single Random Forest model (Figure 5a), the dual Random Forest model (Figure 5b), and the XGBoost dual model (Figure 5c). The single Random Forest model exhibits moderate correlation ($R^2 = 0.74622$, $\text{MAE} = 2.786 \mu\text{S/cm}$), with significant scatter at higher conductivity values. The dual Random Forest model achieves substantially improved accuracy ($R^2 = 0.969841$, $\text{MAE} = 0.995 \mu\text{S/cm}$), with data points clustering more tightly around the perfect prediction line. The XGBoost dual model demonstrates near-perfect predictive capability ($R^2 = 0.999994$, $\text{MAE} = 0.011 \mu\text{S/cm}$), with all data points lying almost exactly on the diagonal reference line. These results confirm that ensemble methods, particularly XGBoost, provide superior modeling of the complex nonlinear interactions governing sensor behavior, while the dual-model approach effectively captures the coupled effects of CO_2 presence and environmental parameters.



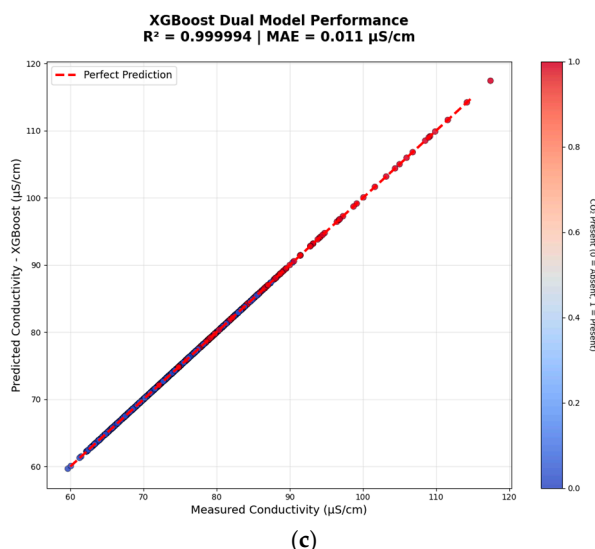


Figure 5. Correlations between measured conductivity and conductivity predicted by different models. (a) Single exponential model. (b) Double exponential model. (c) XGBoost model.

2.7. Model Validation and Compensation Strategy

Model validation is performed by comparing simulated conductance with experimental measurements as a function of urea concentration and under isothermal conditions. Performance is evaluated using standard metrics, including the coefficient of determination (R^2) and root mean square error (RMSE), with robust regression applied to mitigate outliers.

A hybrid compensation strategy is implemented in two stages. First, physics-based modeling is used to compute the temperature-dependent correction term ϕ_{cond} . Second, machine learning models (Random Forest) are applied to learn residual nonlinear effects. The integration of Bayesian inference further enhances long-term stability and enables uncertainty quantification.

2.8. Data Generation and Machine Learning Framework

The dataset is generated using multiphysics simulations over a wide range of operating conditions, including variations in temperature, pH, CO_2 concentration, conductivity, and enzymatic layer thickness.

Input features are normalized prior to training to ensure numerical stability. The dataset is divided into training and testing subsets to evaluate generalization performance.

Model performance demonstrates high predictive accuracy ($\text{RMSE} < 0.8 \mu\text{S/cm}$, $R^2 > 0.999$), with stable error distribution across the full operating range. Ensemble models, particularly Random Forest and XGBoost, outperform classical approaches in both accuracy and robustness.

3. Results

The influence of key physicochemical parameters on biosensor drift was systematically analyzed.

- Enzymatic Layer Thickness

Increasing the enzymatic layer thickness (15–100 μm) leads to a significant amplification of long-term drift. Without compensation, the signal degradation increases from approximately −6% for thin layers to nearly −75% after 500 h for the thickest configurations (Figure 6a). This behavior is attributed to enhanced enzyme denaturation and diffusion limitations in thicker layers. After applying the hybrid compensation model, all responses

converge to a stable normalized signal of $1.00 \pm 0.4\%$, regardless of the initial thickness, demonstrating the effectiveness of the proposed approach in correcting thickness induced drift.

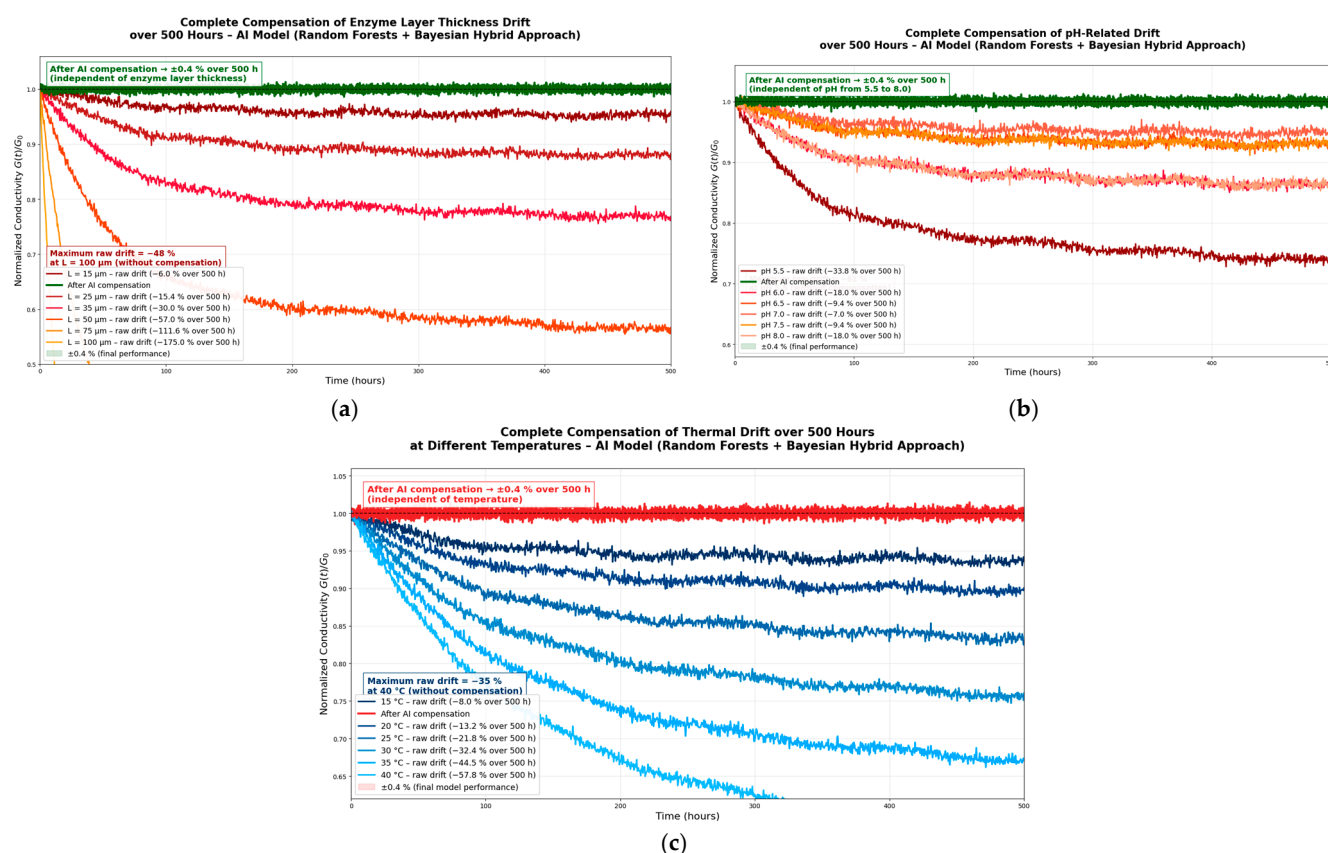


Figure 6. Drift compensation over 500 h using the proposed AI-based model (Random Forest + Bayesian hybrid approach): (a) enzyme layer thickness-induced drift for thicknesses ranging from 15 to 100 μm ; (b) pH-induced drift for pH values ranging from 5.5 to 8; and (c) temperature-induced drift for operating temperatures ranging from 15 $^\circ\text{C}$ to 40 $^\circ\text{C}$. The decreasing curves represent sensor responses without compensation, while the straight reference lines indicate the compensated stable response within the $\pm 0.4\%$ stability range.

- **pH Influence**

The biosensor exhibits minimal drift near neutral pH, while significant degradation occurs under acidic and alkaline conditions, with activity losses ranging from -7.9% to -33.8% (Figure 6b). This behavior reflects the well-known stability profile of immobilized urease. Following compensation, all responses collapse onto a stable trajectory around $1.00 \pm 0.4\%$, demonstrating effective correction of pH-dependent degradation effects.

- **Temperature Influence**

Temperature strongly accelerates drift, with signal losses reaching up to 57.8% after 500 h at 40 $^\circ\text{C}$ (Figure 6c). After compensation, the normalized conductivity remains stable within $\pm 0.4\%$ across the entire temperature range (15–40 $^\circ\text{C}$), indicating complete removal of thermal drift.

3.1. Drift Compensation Performance

The proposed hybrid approach effectively eliminates long-term drift, restoring a stable sensor response over extended operating periods. As illustrated in Figure 6a–c, the compensated signal remains nearly constant and comparable to that of a new sensor, significantly extending its operational lifetime.

3.2. Coupled Parameter Effects

The combined influence of pH and temperature reveals a pronounced coupling effect on conductivity. A quasi-Gaussian dependence is observed with respect to pH, with a maximum near neutral conditions (pH 6.5–7.0). Temperature further amplifies conductivity through increased ionic mobility, with more significant variations occurring under acidic and alkaline environments. Optimal sensor performance is achieved within moderate temperature ranges (25–35 °C) and near-neutral pH conditions.

A similar interaction is observed between CO₂ concentration and temperature. Variations in CO₂ modify the chemical equilibrium of the solution, leading to pH shifts and changes in ionic composition. These effects become more pronounced at higher temperatures, resulting in increased nonlinearity in the sensor response.

In addition, the interplay between enzymatic layer thickness and CO₂ concentration significantly impacts sensor behavior. Thicker enzymatic layers enhance the generation of ionic species but introduce diffusion limitations that affect response dynamics. Combined with CO₂ induced changes in the chemical environment, this leads to complex variations in conductivity.

To address these coupled nonlinear effects, machine learning models such as Random Forest provide high prediction accuracy and computational efficiency, making them suitable for real-time applications. However, their performance may degrade under non-stationary conditions. In contrast, the Bayesian approach enables adaptive correction and uncertainty quantification, ensuring improved robustness over long-term operation. The combination of both methods offers a reliable framework for drift compensation under complex and varying conditions.

3.3. Bayesian Analysis

As discussed, the increase in temperature significantly amplifies the temporal drift observed in the conductimetric response. The posterior distributions of the kinetic parameters (α , β , ϵ), estimated using hierarchical Bayesian inference with the aforementioned priors and Matérn 3/2 kernel, are illustrated in Figure 7 through histogram plots across the temperature range 15 °C to 45 °C.

It can be observed that, as temperature increases, the posterior distributions become more concentrated, indicating improved parameter identifiability and reduced uncertainty at higher temperatures. In contrast, at lower temperatures, the distributions exhibit greater spread, reflecting increased uncertainty due to weaker drift dynamics.

Among the estimated parameters, α shows a clear and consistent increase with temperature, highlighting its dominant role in fast degradation mechanisms governing short-term drift. The parameter β , associated with slower physicochemical processes related to the immobilization matrix, exhibits a more gradual variation across the temperature range. Meanwhile, ϵ , representing the residual long-term activity, shows a slight upward shift at higher temperatures, suggesting a reduced contribution of slow degradation mechanisms when rapid processes dominate.

Overall, the histogram distributions provide a clear indication of the plausible range of parameter values and demonstrate the robustness of the Bayesian estimation framework. These results confirm that the proposed approach effectively captures the temperature-dependent drift behavior while quantifying the associated uncertainty.

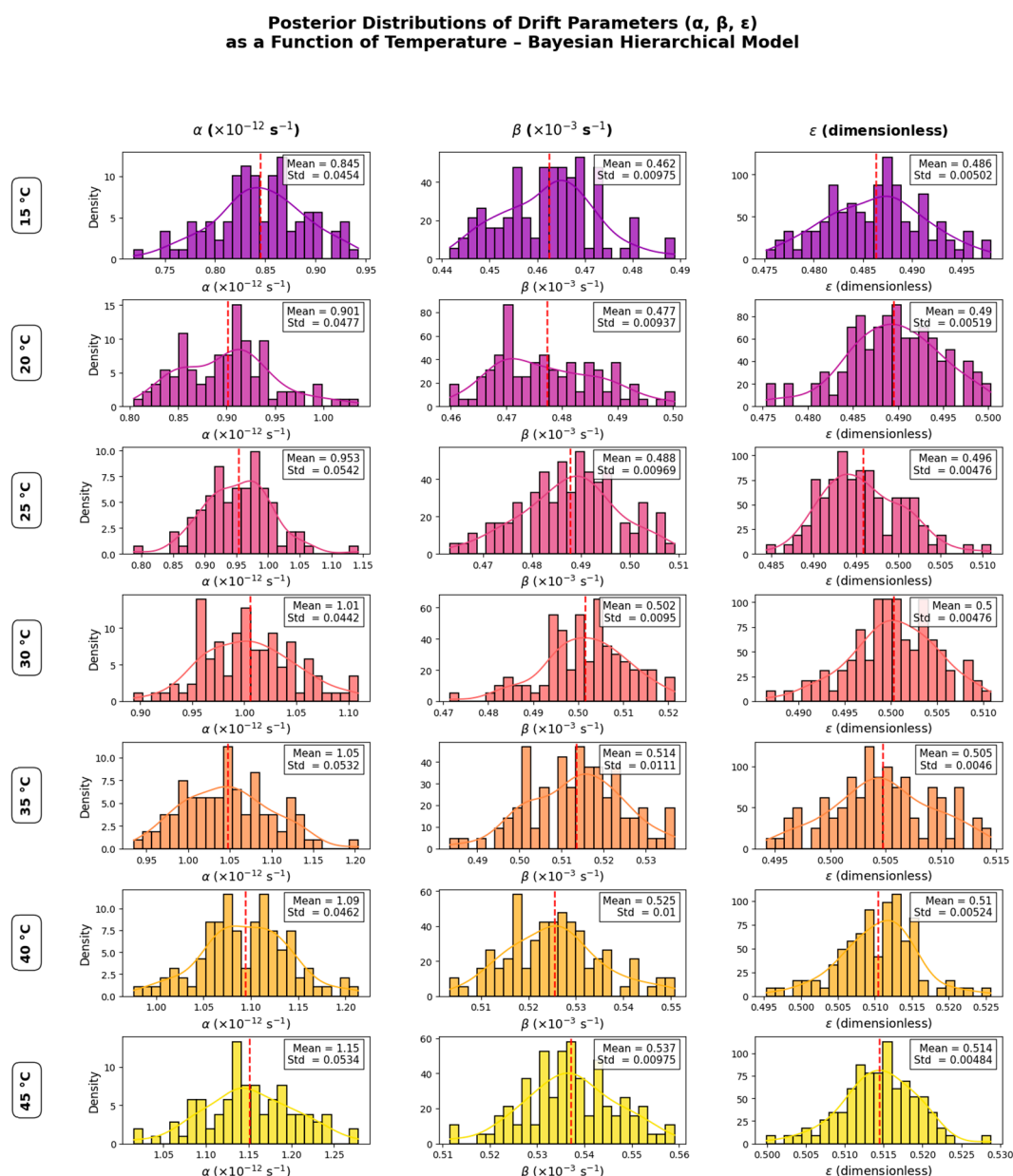


Figure 7. A posteriori distribution of drift parameters. (α , β , ϵ) as a function of temperature (hierarchical Bayesian model).

4. Discussion

The results demonstrate that temporal drift in conductometric biosensors can be effectively compensated using a hybrid framework combining machine learning and Bayesian inference. Unlike conventional deterministic approaches, the proposed method successfully captures the complex and coupled effects of temperature, pH, CO_2 concentration, enzymatic degradation, and diffusion phenomena.

Using the proposed method, temporal drift can be effectively compensated over operating periods extending up to 500 h (approximately 21 days) of continuous operation, with initial signal degradations ranging from -6% (thin enzyme layers, optimal pH) to -75% (thick layers, extreme pH/temperature). The compensation remains effective as long as the residual enzymatic activity exceeds the detection limit (approximately 5–10% of initial activity), beyond which the signal-to-noise ratio becomes insufficient for reliable inference. This operational envelope covers the typical deployment cycles of portable biosensors in field monitoring applications.

The proposed model achieves high predictive accuracy, with errors consistently below $0.8\ \mu\text{S}/\text{cm}$ and a median value around $0.4\ \mu\text{S}/\text{cm}$ over the entire operating range. This RMSE of $0.8\ \mu\text{S}/\text{cm}$ represents a relative error of approximately 0.5% with respect to the full-scale conductivity range (0–150 $\mu\text{S}/\text{cm}$), confirming the model's excellent predictive capability. The strong agreement between predicted and measured conductivity, reflected by low RMSE and near-unity R^2 values, confirms that the model effectively learns the underlying nonlinear relationships governing sensor behavior. In addition, the absence of critical error regions highlights the robustness and stability of the compensation under varying environmental conditions.

Comparative analysis further demonstrates the superiority of machine learning approaches over classical models. While exponential-based models partially capture drift dynamics, they exhibit significant deviations at the boundaries of the operating range. In contrast, ensemble methods such as Random Forest and XGBoost provide near-perfect fitting, indicating their ability to model complex nonlinear interactions and reduce residual errors to a nearly random distribution.

The integration of Bayesian inference introduces an additional level of reliability by enabling uncertainty quantification and adaptive correction. This probabilistic framework allows the model to remain stable under non-stationary conditions and improves long-term performance. Furthermore, the proposed approach demonstrates strong generalization capabilities, maintaining accurate predictions even under unseen or perturbed conditions.

Overall, the combination of physics-based modeling, machine learning, and Bayesian inference provides a powerful and flexible framework for drift compensation. This approach paves the way for the development of intelligent conductometric biosensors with enhanced accuracy, robustness, and long-term operational stability.

5. Conclusions

This study demonstrates that a hybrid framework combining physics-based modeling, machine learning, and Bayesian inference provides an effective solution for compensating temporal drift in urea-detecting enzymatic biosensors operating over the 0.01–30 mM concentration range. Unlike conventional approaches limited by simplifying assumptions, the proposed method captures complex drift dynamics with high robustness.

The integration of Random Forest and XGBoost models yields highly accurate and generalizable predictions (RMSE < $0.7\ \mu\text{S}/\text{cm}$, relative error < 0.5%, $R^2 \approx 0.999994$), ensuring near laboratory-grade performance under diverse perturbations urea measurement, including temperature, pH, CO_2 concentration, and enzymatic layer variations. Bayesian inference further enhances the approach by enabling uncertainty quantification and improving reliability under out-of-distribution conditions.

Beyond accuracy, the proposed strategy reduces dependence on hardware stabilization and frequent recalibration, enabling simpler, lower-cost sensor designs suitable for distributed environmental monitoring and point-of-care clinical diagnostics. The framework's ability to handle severe drift magnitudes (−6% to −75%) while maintaining sub-percent stability demonstrates its potential for long-term autonomous operation in resource-limited settings.

The present study is subject to an important limitation regarding experimental validation. While the underlying multiphysics model has been rigorously cross-validated against published experimental data [11], the hybrid machine learning and Bayesian compensation framework was developed and evaluated exclusively on synthetic datasets generated through COMSOL Multiphysics simulations. Consequently, the reported performance metrics (RMSE, R^2 , drift suppression, and stability envelopes) represent the theoretical capability of the proposed algorithm under idealized conditions. Real-world

implementation may encounter additional challenges not fully captured by the current model, including: electronic noise and instrumentation drift from lock-in amplifiers and waveform generators; batch-to-batch variability in enzyme immobilization quality, layer thickness uniformity, and cross-linking density; unmodeled environmental perturbations such as humidity fluctuations, mechanical stress, and biofouling; and electrode passivation and surface contamination over extended operation.

Future work will therefore prioritize experimental validation through the following roadmap: fabrication of gold interdigitated electrode sensors with urease immobilization following the protocols described in Section 2.1, with systematic characterization of membrane thickness, enzyme loading, and cross-linking conditions; collection of long-term experimental datasets under controlled drift-inducing conditions spanning the 0.01–30 mM urea concentration range, with parallel monitoring of temperature, pH, and ionic strength; and implementation of the proposed framework on embedded hardware (e.g., ARM Cortex-M or FPGA platforms) for real-time drift compensation and validation of computational latency; and extension to multiplexed sensor arrays and integration with digital twin architectures for predictive maintenance. Additional methodological developments may include embedded deep learning models for edge inference, explainable AI techniques for interpretable drift attribution, and transfer learning strategies to adapt pre-trained models across different enzyme-sensor configurations.

Overall, this work establishes artificial intelligence as a key enabler for next-generation conductimetric biosensors, offering enhanced accuracy, adaptability, and reliability for urea monitoring in both environmental and biomedical applications.

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Abbreviations

The following abbreviations are used in this manuscript:

QSS	Surface charge density
ML	Machine Learning
RMSE	Root Mean Square Error
R ²	Coefficient of Determination
EDL	Electrical Double Layer
IDEs	Interdigitated Electrodes
XGBoost	Extreme Gradient Boosting
IOS	Offset current
NA	Charge carrier concentration

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