

Article

Physics-Informed Stochastic Modeling of Temperature Dynamics and Product Degradation in Cold Chains

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Abstract

The integrity of cold chains is critical for preserving the quality, safety, and efficacy of temperature-sensitive products, including pharmaceuticals, vaccines, and perishable goods. However, real-world cold-chain operations are subject to environmental variability, operational disturbances, and transport-related uncertainties that are often inadequately captured by deterministic models. This study presents a stochastic modeling methodology that integrates a physics-based heat-transfer model with a machine-learning residual correction to predict temperature dynamics and product degradation under uncertainty. Temperature evolution is represented through a stochastic heat-transfer model incorporating random perturbations, while product degradation is quantified using Arrhenius-based kinetics that link thermal exposure to quality loss. A machine-learning-based residual correction is subsequently incorporated to improve predictive accuracy while preserving the physical structure of the governing model. The proposed methodology is evaluated through computational experiments using a representative pharmaceutical cold-chain transportation scenario. Numerical experiments based on the Euler–Maruyama method and Monte Carlo analysis are performed to assess the proposed methodology under representative operating conditions. Results indicate that stochastic variability can produce transient temperature excursions even when average operating conditions remain acceptable, leading to increased degradation and higher failure probabilities. The computational results demonstrate the feasibility of the proposed methodology for the probabilistic estimation of thermal risk and product quality deterioration by integrating physics-based modeling, uncertainty analysis, and data-driven residual correction within a unified computational methodology. The proposed methodology provides a computational basis for the future development of intelligent cold-chain monitoring and decision-support systems. Overall, it offers practical capabilities for uncertainty quantification, reliability assessment, and informed decision making in temperature-sensitive supply chains.



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1. Introduction

Cold chains play a critical role in preserving the quality, safety, and efficacy of temperature-sensitive products, including pharmaceuticals, vaccines, and perishable food items. The increasing globalization of supply networks and the growing demand for

biopharmaceutical products have intensified the need for robust and reliable temperature-controlled systems [1–3]. However, maintaining strict thermal conditions throughout transportation and storage remains a significant challenge due to environmental variability, operational uncertainties, and infrastructure limitations [4].

Previous research has extensively investigated optimization and decision-support strategies for cold-chain operations, particularly in the areas of distribution planning, inventory management, and transportation efficiency [5]. For example, Perez Lechuga et al. [6] developed a real-world optimization framework combining clustering, vehicle routing, and mixed-integer programming to support large-scale pharmaceutical distribution. Such studies highlight the operational complexity of cold-chain systems and the need for advanced analytical tools capable of supporting decision-making under realistic conditions.

More recently, subsequent studies have emphasized the importance of integrated modeling approaches that consider multiple interacting components within the cold chain, including transportation, routing, and system-level decision processes under realistic constraints. Despite these advances, most existing works focus primarily on deterministic optimization and operational efficiency, often neglecting the stochastic nature of temperature dynamics and the direct relationship between thermal exposure and product degradation. This limitation highlights the need for modeling frameworks that explicitly incorporate uncertainty, physical processes, and product-specific degradation mechanisms into cold-chain analysis [7–9].

Despite these advances, most existing cold-chain studies focus either on logistics optimization or on deterministic thermal analyses, while relatively few integrate stochastic physical modeling, uncertainty quantification, product degradation, and data-driven prediction within a unified computational methodology. Recent advances in physics-informed machine learning and digital-twin technologies [10–12] have further emphasized the importance of combining first-principles models with data-driven techniques to improve predictive capability under realistic operating conditions. In contrast, traditional deterministic approaches generally assume stable environmental conditions and predictable operations, limiting their ability to represent the variability introduced by temperature fluctuations, transportation delays, and handling disruptions that may significantly affect product quality [13]. Stochastic modeling provides a natural alternative by explicitly representing uncertainty through stochastic differential equations [14,15], thereby enabling probabilistic assessment of thermal excursions and their impact on product integrity [5]. These considerations motivate the development of integrated methodologies capable of consistently coupling thermal dynamics, uncertainty propagation, quality degradation, and predictive analytics within a unified probabilistic formulation.

Advances in materials science have significantly improved the thermal performance of cold-chain packaging through the development of insulation materials and phase change materials (PCMs), which help stabilize internal temperatures and reduce thermal excursions [16,17]. These thermal properties, including low thermal conductivity and high latent heat capacity, contribute to maintaining temperature-sensitive products within acceptable ranges during transportation. Nevertheless, their effectiveness depends on the complex interaction between material properties, environmental disturbances, and operational conditions [18,19]. Consequently, accurately predicting the thermal behavior of cold-chain systems remains challenging, and deterministic thermal analyses alone are often insufficient to quantify the uncertainty associated with realistic transportation scenarios. This limitation motivates the use of stochastic formulations [14,15] that explicitly represent uncertainty and its propagation while remaining compatible with degradation models, probabilistic risk assessment, and data-driven predictive methodologies [10].

Another crucial aspect of cold-chain performance is the chemical stability of transported products, particularly pharmaceuticals and biological materials whose degradation rates are strongly influenced by thermal exposure. The Arrhenius equation has been widely used to describe temperature-dependent reaction kinetics, providing a quantitative relationship between temperature and degradation rates [8,9]. Incorporating degradation kinetics into cold-chain analysis enables a more realistic assessment of product quality over time, moving beyond simple compliance with temperature thresholds [20]. More recently, artificial intelligence (AI) and machine learning (ML) techniques have complemented these physics-based approaches by enhancing monitoring, prediction, and decision support. Data-driven models, including Long Short-Term Memory (LSTM) networks, ensemble learning methods such as Random Forest and Gradient Boosting, and reinforcement learning algorithms, have demonstrated promising capabilities for temperature forecasting, anomaly detection, risk classification, and adaptive decision making under uncertain operating conditions [21–25].

Recent studies have highlighted the importance of explicitly accounting for uncertainty in logistics systems, particularly in routing and time-window problems where variability in demand, travel times, and unloading operations can significantly affect system performance [6]. These findings reinforce the need for analytical methodologies that integrate physical processes, stochastic variability, and product degradation within a unified mathematical formulation. Although significant advances have been achieved in cold-chain management, existing approaches often emphasize either deterministic physical modeling or purely data-driven prediction, thereby limiting their ability to accurately represent the complex interactions governing temperature evolution and quality deterioration under realistic operating conditions [10].

Substantial progress has been achieved in stochastic temperature modeling, pharmaceutical degradation analysis, uncertainty quantification, hybrid physics-based modeling, and data-driven prediction for cold-chain applications [3,26–30]. To better position the methodological contribution of the present study within this body of work, Table 1 summarizes the principal methodological limitations identified in representative studies together with the corresponding contributions of the proposed methodology. This comparison highlights how the different components of the presented approach collectively address existing gaps beyond the independent application of individual techniques.

This study develops a stochastic modeling methodology that integrates a physics-based heat-transfer model with a machine-learning residual correction to analyze temperature dynamics and product degradation in cold chains under uncertainty.

The main contributions of this work can be summarized as follows.

1. A unified stochastic methodology is developed by integrating a physics-based heat-transfer model, environmental uncertainty, and temperature-dependent degradation kinetics into a single mathematical formulation for pharmaceutical cold-chain systems.
2. The proposed methodology couples stochastic temperature prediction with Arrhenius-based degradation modeling, enabling uncertainty propagation to be quantified and its impact on product quality and system reliability to be systematically assessed.
3. A machine-learning residual correction is incorporated to complement the physics-based model by capturing systematic nonlinear prediction errors while preserving the physical interpretability of the governing equations.
4. An integrated analytical framework combining stochastic differential equations, Monte Carlo simulation, degradation modeling, and machine-learning residual correction is established to support probabilistic quality assessment, uncertainty quantification, and risk-informed decision-making in pharmaceutical cold-chain management.

Table 1. Methodological positioning of the proposed approach relative to representative limitations in existing cold-chain modeling studies.

Research Aspect	Limitation in Previous Studies	Main Contribution
Thermal dynamics	Deterministic formulations commonly represent temperature evolution without explicitly accounting for environmental uncertainty.	Temperature evolution is modeled through stochastic differential equations, enabling random environmental disturbances to be explicitly incorporated into the thermal dynamics.
Product degradation	Existing approaches frequently analyze temperature evolution and quality degradation independently.	The stochastic temperature model is directly coupled with Arrhenius degradation kinetics, thereby allowing thermal uncertainty to propagate continuously into product quality predictions.
Uncertainty analysis	Most studies evaluate isolated sources of uncertainty without quantifying their cumulative effect on final product quality.	Monte Carlo simulation propagates uncertainty throughout the transportation process, providing probabilistic estimates of degradation kinetics, associated quality loss, and failure risk.
Machine learning	Data-driven models often operate as black-box predictors with limited physical interpretability.	A residual machine-learning framework is integrated as a complementary component that respects the governing physical model while improving predictive accuracy.
System integration	Existing studies typically address individual modeling components rather than an integrated computational methodology.	The proposed framework unifies stochastic heat transfer, Arrhenius degradation, uncertainty propagation, and residual learning into a single computational architecture for cold-chain risk assessment.

The remainder of this paper is organized as follows. Section 2 presents the proposed stochastic model together with its mathematical formulation. Section 3 describes the numerical simulation procedure and the stochastic analysis of temperature dynamics and product degradation. Section 4 introduces the machine-learning enhancement, presents the hybrid model validation, and evaluates its predictive performance using both controlled numerical experiments and a case study based on real cold-chain temperature data. Section 5 discusses the main findings, practical implications, and limitations of the proposed methodology. Finally, Section 6 summarizes the principal conclusions and outlines directions for future research.

2. Mathematical Formulation

This section presents the theoretical foundations of the proposed stochastic methodology for modeling temperature dynamics and product degradation in pharmaceutical cold chains under uncertainty. The proposed framework unifies physics-based heat transfer, stochastic processes, degradation kinetics, and a machine-learning residual correction into a unified probabilistic formulation to characterize temperature evolution, uncertainty propagation, and product degradation for systematic reliability assessment.

2.1. Notation and Definitions

To facilitate the presentation of the mathematical model, the principal symbols, their definitions, and the corresponding units used throughout the manuscript are summarized below.

$t \equiv$ Time (s, h).

$T(t) \equiv$ Product temperature at time t (K or °C).

$T_{\text{amb}}(t) \equiv$ Ambient temperature surrounding the product (K or °C).

$T_0 \equiv$ Initial product temperature (K or °C).

$\mu(t, T) \equiv$ Drift coefficient describing the deterministic component of the stochastic temperature process (K s^{-1}).

$\sigma(t, T) \equiv$ Diffusion coefficient representing stochastic variability ($\text{K s}^{-1/2}$).
 $W(t) \equiv$ Standard Wiener process ($\text{s}^{1/2}$).
 $\lambda \equiv$ Thermal conductivity ($\text{W m}^{-1} \text{K}^{-1}$).
 $q \equiv$ Heat flux (W m^{-2}).
 $\rho \equiv$ Product density (kg m^{-3}).
 $c_p \equiv$ Specific heat capacity ($\text{J kg}^{-1} \text{K}^{-1}$).
 $\nabla T \equiv$ Temperature gradient (K m^{-1}).
 $k_{\text{chem}} \equiv$ Reaction rate constant (s^{-1}).
 $A_s \equiv$ Effective heat-transfer surface area (m^2).
 $Q(t) \equiv$ Dimensionless product quality index.
 $Q_0 \equiv$ Initial product quality.
 $A \equiv$ Arrhenius pre-exponential factor (s^{-1}).
 $E_a \equiv$ Activation energy (J mol^{-1}).
 $R \equiv$ Universal gas constant ($\text{J mol}^{-1} \text{K}^{-1}$).
 $X \equiv$ Feature vector containing relevant environmental, operational, and thermal variables.
 $L \equiv$ Characteristic thickness of the insulation layer (m).
 $C_{\text{eff}} \equiv$ Effective thermal capacitance (J K^{-1}).
 $T_{\text{pred}}(t) \equiv$ Hybrid temperature prediction obtained by combining the stochastic heat-transfer model with the machine-learning correction.
 $e(t) \equiv$ Prediction residual between the stochastic model prediction and the observed temperature.
 $f_{\text{ML}}(X) \equiv$ Machine-learning prediction or correction function.
 $T_{\text{crit}} \equiv$ Critical temperature threshold (K).
 $\mathbb{P}(\cdot) \equiv$ Probability measure associated with events defined on the probability space.
 $T_{\text{obs}}(t) \equiv$ Observed product temperature obtained from measurements.

The stochastic temperature model is formulated on a filtered probability space, which provides the mathematical framework for representing random variables, stochastic processes, and the evolution of uncertainty over time. Specifically, let

$$(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, \mathbb{P})$$

denote a filtered probability space, where Ω is the sample space, $\mathcal{F}$ is the associated σ -algebra, $\{\mathcal{F}_t\}_{t \geq 0}$ is a filtration satisfying the usual conditions, and $\mathbb{P}$ is the probability measure.

Random perturbations arising from environmental variability, transportation disturbances, and operational uncertainties are represented by a standard Wiener process $W(t)$ adapted to the filtration $\{\mathcal{F}_t\}_{t \geq 0}$. This probabilistic structure establishes the mathematical foundation for modeling the stochastic thermal behavior encountered in practical cold-chain operations.

The mathematical formulation developed in the following subsections combines first-principles heat-transfer mechanisms with stochastic processes to provide a physically interpretable representation of temperature evolution under uncertainty. This formulation establishes the theoretical basis for the subsequent development of the degradation model, the physics-informed machine-learning correction, and the probabilistic reliability analysis.

2.2. Physics-Based Stochastic Temperature Model

Temperature variations in cold-chain systems are inherently stochastic due to environmental fluctuations, transportation disturbances, and operational uncertainties. To represent these effects, temperature evolution is modeled within the probabilistic structure introduced in the previous subsection. The resulting thermal dynamics are formulated as follows:

$$(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, \mathbb{P}),$$

where the Wiener process $W(t)$ drives the stochastic perturbations. Consequently, this mathematical formulation allows for the direct integration of environmental and operational uncertainties into the temperature evolution process [14,15].

Under this probabilistic specification, the stochastic model generates a family of admissible temperature trajectories. Individual realizations describe possible thermal evolutions, while the collective ensemble characterizes the uncertainty associated with the temperature dynamics.

The thermal response of cold-chain systems depends on both the thermophysical properties of the packaging materials and the surrounding operating conditions. Advanced insulation materials and phase change materials (PCMs) improve thermal stability by increasing the effective thermal inertia of the system to reduce temperature excursions during transportation [16,17].

Although Fourier's law provides the fundamental description of conductive heat transfer, it does not account for the variability observed during real-world transportation. This limitation motivates the incorporation of stochastic terms into the temperature model.

Accordingly, the product temperature is modeled as the Itô stochastic process satisfying

$$dT(t) = \mu(t, T(t)) dt + \sigma(t, T(t)) dW(t), \quad (1)$$

where the drift coefficient $\mu(t, T(t))$ represents the deterministic component of the temperature dynamics, while the diffusion coefficient $\sigma(t, T(t))$ quantifies the intensity of the stochastic fluctuations. The Wiener process $W(t)$ models the random perturbations governing the probabilistic evolution of the temperature.

Equation (1) extends the classical heat-transfer model by incorporating uncertainty through the diffusion term while preserving the physical interpretation of the deterministic core.

This stochastic representation models the probabilistic description of temperature evolution, enabling the quantification of thermal uncertainty and the assessment of its impact on product quality and degradation [5].

2.3. Chemical Degradation Kinetics

The stability of temperature-sensitive products is strongly influenced by chemical degradation processes. Since their quality is directly affected by thermal exposure, such kinetics are incorporated into the proposed mathematical model through an Arrhenius-type formulation. The reaction rate constant is denoted by k_{chem} and is defined as

$$k_{\text{chem}} = A \exp\left(-\frac{E_a}{RT}\right), \quad (2)$$

where A is the pre-exponential factor, E_a is the activation energy, R is the universal gas constant, and T denotes the absolute temperature. This relationship establishes the dependence of the reaction rate on the absolute temperature and has been widely employed in the analysis of food, pharmaceutical, and biological products subjected to varying thermal conditions [8,9].

The classical Arrhenius equation assumes a single dominant thermally activated degradation mechanism and has been widely validated as an effective approximation for these materials under controlled storage conditions. For products exhibiting multiple degradation pathways or additional environmental effects, such as humidity, oxygen

concentration, light exposure, or mechanical stress, the proposed formulation can be extended by incorporating product-specific kinetic models. Consequently, the Arrhenius model adopted here should be regarded as a physically meaningful baseline that provides a flexible platform for uncertainty analysis and future model extensions.

By coupling the stochastic temperature model with Arrhenius-based degradation kinetics, the proposed formulation establishes a direct link between thermal variability and product quality deterioration, enabling the probabilistic assessment of shelf-life reduction under uncertain operating conditions.

2.4. Hybrid Modeling Architecture

The stochastic temperature model captures the dominant physical mechanisms governing temperature evolution. To account for residual nonlinear effects not explicitly represented by the governing equations, a machine-learning residual correction is incorporated into the physics-based stochastic formulation [10]. The physical model describes the underlying thermal dynamics, whereas the machine-learning component learns the residual prediction errors from observational data, thereby improving predictive accuracy while preserving physical interpretability.

$$T_{\text{pred}}(t) = T_{\text{stochastic}}(t) + f_{\text{ML}}(X_t), \quad (3)$$

where $T_{\text{stochastic}}(t)$ denotes the temperature predicted by the stochastic heat-transfer model, $T_{\text{pred}}(t)$ is the corresponding hybrid prediction, and $f_{\text{ML}}(X_t)$ represents the residual correction estimated from the feature vector X_t . This time-dependent vector is constructed as

$$X_t = (T_{\text{amb}}(t), \tau_t, R_t, N_t, \eta_t, \dots),$$

where its components describe the thermal and operational state of the cold-chain system. In general,

$$f_{\text{ML}} : \mathbb{R}^p \rightarrow \mathbb{R},$$

with p denoting the number of explanatory variables. The learning objective is to approximate the residual error of the stochastic model,

$$f_{\text{ML}}(X_t) \approx T_{\text{obs}}(t) - T_{\text{stochastic}}(t),$$

using supervised training on historical or observed temperature data. Consequently, the hybrid model preserves the physical interpretation of the governing equations while it improves predictive accuracy through the estimation of nonlinear residual effects. Depending on the application, the mapping f_{ML} may be approximated using regression models, ensemble-learning methods, or deep neural networks, such as Random Forest and Long Short-Term Memory (LSTM) architectures.

Equation (1) admits the equivalent integral representation

$$T_{\text{stochastic}}(t) = T_0 + \int_0^t \mu(s, T(s)) ds + \int_0^t \sigma(s, T(s)) dW(s), \quad (4)$$

where T_0 denotes the initial product temperature. The first integral describes the cumulative deterministic heat transfer, whereas the Itô integral represents the accumulated stochastic perturbations. Consequently, $T_{\text{stochastic}}(t)$ provides the physics-based temperature prediction used as the baseline for the subsequent residual correction.

The machine-learning model estimates the residual error of the stochastic prediction, accounting for nonlinear effects and model discrepancies that are difficult to represent

analytically. The resulting hybrid formulation combines first-principles stochastic modeling with supervised residual learning, which improves predictive accuracy while preserving the physical interpretation of the governing equations.

Monte Carlo simulation is employed to generate multiple realizations of the stochastic temperature process defined in Equation (1). The resulting ensemble of temperature trajectories allows researchers to estimate probabilistic performance measures, reliability indicators, and thermal risk.

$$\mathbb{P}\left(\sup_{t \in [0, T]} T(t) > T_{\text{crit}}\right), \quad (5)$$

where T_{crit} denotes the maximum admissible product temperature. The probability in Equation (5) quantifies the risk of exceeding the prescribed temperature limit and serves as a measure of thermal reliability. Such probabilistic metrics support systematic reliability assessment and risk-informed decision making in temperature-sensitive supply chains [31,32].

The hybrid methodology combines stochastic heat-transfer modeling, Arrhenius-based degradation kinetics, machine-learning residual correction, and Monte Carlo simulation into a unified probabilistic model. Equations (1)–(3) define the temperature dynamics, the degradation kinetics, and the hybrid prediction, respectively, whereas the simulation step quantifies uncertainty and thermal reliability.

Consequently, the drift term in Equation (1) is given by

$$\mu(t, T) = \frac{\lambda A_s}{L C_{\text{eff}}} (T_{\text{amb}}(t) - T(t)), \quad (6)$$

which relates the stochastic model to the underlying heat-transfer physics.

Substitution of Equation (6) into Equation (1) yields the following expression for the temperature dynamics:

$$dT(t) = \frac{\lambda A_s}{L C_{\text{eff}}} (T_{\text{amb}}(t) - T(t)) dt + \sigma(t, T(t)) dW(t), \quad T(0) = T_0. \quad (7)$$

where the first term describes the deterministic heat-transfer dynamics and the second term represents the stochastic diffusion. Equation (7) defines the stochastic temperature model adopted throughout the remainder of this work.

Once the temperature trajectory $T(t)$ has been obtained from Equation (7), it defines the thermal history governing product degradation. Since chemical and biochemical reactions are temperature-dependent, the Arrhenius relation in Equation (2) yields the instantaneous reaction rate as

$$k_{\text{chem}}(t) = A \exp\left(-\frac{E_a}{R T(t)}\right), \quad (8)$$

Each realization of the stochastic temperature process therefore generates a corresponding reaction-rate trajectory, which allows thermal uncertainty to propagate naturally into the degradation kinetics. This coupling establishes the connection between stochastic temperature evolution and product quality through a physically interpretable kinetic model.

To quantify the cumulative effect of thermal exposure, let $D(t)$ denote the cumulative degradation state. Assuming continuous accumulation according to the instantaneous reaction rate, the evolution of this state is governed by

$$\frac{dD(t)}{dt} = k_{\text{chem}}(t), \quad (9)$$

subject to the initial condition

$$D(0) = 0. \quad (10)$$

Substitution of Equation (8) into Equation (9), followed by integration over the time interval $[0, t]$, yields the cumulative degradation equation:

$$D(t) = \int_0^t A \exp\left(-\frac{E_a}{R T(\tau)}\right) d\tau, \quad (11)$$

which represents the cumulative degradation associated with the thermal history of the product. Since the reaction rate depends exponentially on temperature through the Arrhenius relation, short-term temperature excursions may produce a disproportionate contribution to the accumulated degradation. Consequently, the degradation process depends not only on the average temperature but also on the magnitude and duration of thermal fluctuations. This formulation establishes the quantitative link between stochastic temperature evolution and product degradation, forming the groundwork for the probabilistic quality assessment presented in the following sections.

Because $T(t)$ is a stochastic process, the degradation rate $k_{\text{chem}}(t)$ is also stochastic and time-dependent. Consequently, the accumulated degradation is determined by the entire temperature trajectory rather than by a single deterministic value.

While Equation (11) describes the accumulated degradation, it is often convenient to express the product condition in terms of a normalized quality index. Let $Q(t)$ denote a dimensionless quality variable, where $Q(0) = 1$ represents the initial product quality. Assuming first-order degradation kinetics, the evolution of this quality index is governed by

$$\frac{dQ(t)}{dt} = -k_{\text{chem}}(t) Q(t), \quad (12)$$

which, together with the initial condition $Q(0) = 1$, admits the closed-form solution

$$Q(t) = \exp\left(-\int_0^t A \exp\left(-\frac{E_a}{R T(s)}\right) ds\right). \quad (13)$$

Equation (13) establishes the relationship between stochastic temperature evolution and product quality. Throughout this work, $Q(t)$ denotes a normalized dimensionless product quality index representing the remaining quality of the pharmaceutical product relative to its initial condition. Accordingly, $Q(0) = 1$ corresponds to an undegraded product, whereas decreasing values indicate progressive quality loss resulting from cumulative thermal exposure. The degradation variable $D(t)$ defined in Equation (11) represents the cumulative thermal degradation state, while the quality index is obtained through the corresponding first-order degradation model. Since the degradation rate depends exponentially on temperature through the Arrhenius relation, the remaining product quality is determined by the complete thermal history rather than by isolated temperature measurements. Consequently, even relatively small but persistent temperature excursions may accumulate over time and produce substantial quality deterioration. For the representative pharmaceutical transportation scenario considered in this study, a minimum acceptable quality threshold of $Q_{\min} = 0.90$ is adopted to distinguish acceptable products from those requiring rejection. Accordingly, products satisfying $Q(t) \geq Q_{\min}$ are considered to preserve their required quality throughout transportation. Although the stochastic heat-transfer and degradation models capture the dominant physical mechanisms, practical cold-chain operations may involve additional nonlinear effects that are difficult to represent analytically. To account for these effects, the machine-learning correction introduced in Equation (3) is incorporated as a residual component based on the feature vector X_t . This

data-driven correction refines the stochastic prediction by learning systematic discrepancies between the modeled and observed temperatures, thereby improving predictive accuracy while preserving the physical interpretation of the governing equations.

In practical applications, the temperature prediction is obtained by combining the stochastic heat-transfer model with the machine-learning residual correction introduced in Equation (3). Accordingly, the hybrid prediction is expressed as $T_{\text{pred}}(t) = T_{\text{stochastic}}(t) + f_{\text{ML}}(X_t)$. The practical implementation of this hybrid prediction, including the training of the machine-learning model, the construction of the feature vector, and its integration with the stochastic simulations, is described in the following section.

2.4.1. Assumptions

To establish the well-posedness of the proposed stochastic temperature model, we introduce the following standard regularity assumptions. For the mathematical analysis, the stochastic differential equation defined in Equation (1) is written in the general representation:

$$dT(t) = b(t, T(t), X_t) dt + \Sigma(t, T(t), X_t) dW(t),$$

where $b(t, T, X_t)$ and $\Sigma(t, T, X_t)$ denote the drift and diffusion coefficients, respectively. In this mathematical specification, the drift coefficient b corresponds to the deterministic heat-transfer term introduced in Equation (6), whereas Σ characterizes the stochastic diffusion coefficient that accounts for environmental and operational uncertainty.

Assumption 1 (Measurability). *The ambient temperature process $T_{\text{amb}}(t)$ and the feature vector X_t are progressively measurable with respect to the filtration $\{\mathcal{F}_t\}_{t \geq 0}$.*

Assumption 2 (Lipschitz continuity). *There exist constants $L_b > 0$ and $L_\Sigma > 0$ such that, for all $t \geq 0$, $x \in \mathbb{R}^m$, and $T_1, T_2 \in \mathbb{R}$,*

$$|b(t, T_1, x) - b(t, T_2, x)| \leq L_b |T_1 - T_2|, \quad (14)$$

and

$$|\Sigma(t, T_1, x) - \Sigma(t, T_2, x)| \leq L_\Sigma |T_1 - T_2|. \quad (15)$$

Assumption 3 (Linear growth). *There exists a constant $C > 0$ such that, for all $t \geq 0$, $x \in \mathbb{R}^m$, and $T \in \mathbb{R}$,*

$$|b(t, T, x)|^2 + |\Sigma(t, T, x)|^2 \leq C(1 + |T|^2). \quad (16)$$

Assumption 4 (Positive thermal regime). *There exists a constant $T_{\min} > 0$ such that, almost surely,*

$$T(t) \geq T_{\min} > 0, \quad t \in [0, t_f]. \quad (17)$$

This condition is physically justified because temperature is expressed on the absolute Kelvin scale, where thermodynamic states remain strictly positive throughout the operating regime considered in this study.

Assumptions A1–A3 are standard regularity conditions in the theory of stochastic differential equations and guarantee the existence and uniqueness of a strong Itô solution under the classical probabilistic setting [14,15]. Assumption A4 ensures that the Arrhenius degradation model defined in Equation (2) remains well defined throughout the simulation horizon, thereby preserving the physical consistency of the coupled stochastic kinetics.

2.4.2. Existence and Uniqueness of the Temperature Process

We begin by proving the existence and uniqueness of strong solutions for the proposed stochastic temperature model.

Theorem 1 (Existence and uniqueness of the temperature process). *Suppose that Assumptions A1–A3 hold. Then, for every square-integrable initial condition*

$$T_0 \in L^2(\Omega, \mathcal{F}_0, \mathbb{P}),$$

the stochastic differential equation (7) admits a unique strong Itô solution on the interval $[0, t_f]$. Moreover, the solution process satisfies

$$T \in L^2(\Omega; C([0, t_f])),$$

with the second moment satisfying the bound

$$\mathbb{E} \left[\sup_{0 \leq t \leq t_f} |T(t)|^2 \right] < \infty. \quad (18)$$

Proof. By Assumption 1, the processes $T_{\text{amb}}(t)$ and X_t are progressively measurable. Hence, the coefficients $b(t, T, X_t)$ and $\Sigma(t, T, X_t)$ are progressively measurable stochastic processes for each fixed state variable T .

Assumption 2 implies that both coefficients satisfy the global Lipschitz condition with respect to the temperature variable. More precisely, there exists a constant $L > 0$ such that, for all $T_1, T_2 \in \mathbb{R}$,

$$|b(t, T_1, X_t) - b(t, T_2, X_t)|^2 + |\Sigma(t, T_1, X_t) - \Sigma(t, T_2, X_t)|^2 \leq L|T_1 - T_2|^2,$$

almost surely. Assumption 3 provides the corresponding linear growth condition,

$$|b(t, T, X_t)|^2 + |\Sigma(t, T, X_t)|^2 \leq C(1 + |T|^2).$$

Therefore, the classical existence and uniqueness theorem for Itô stochastic differential equations applies, yielding a unique strong Itô solution $T(t)$ on the interval $[0, t_f]$.

It remains to establish the moment estimate. From the integral representation of the stochastic differential equation,

$$T(t) = T_0 + \int_0^t b(s, T(s), X_s) ds + \int_0^t \Sigma(s, T(s), X_s) dW(s),$$

we obtain, for $0 \leq t \leq t_f$,

$$\sup_{0 \leq r \leq t} |T(r)|^2 \leq 3|T_0|^2 + 3 \sup_{0 \leq r \leq t} \left| \int_0^r b(s, T(s), X_s) ds \right|^2 + 3 \sup_{0 \leq r \leq t} \left| \int_0^r \Sigma(s, T(s), X_s) dW(s) \right|^2.$$

Using the Cauchy–Schwarz inequality for the deterministic integral and the Burkholder–Davis–Gundy inequality for the stochastic integral, there exists a positive constant C_T , depending only on the final time t_f but independent of t , such that

$$\mathbb{E} \left[\sup_{0 \leq r \leq t} |T(r)|^2 \right] \leq C_T \left(\mathbb{E}|T_0|^2 + \int_0^t \mathbb{E} \left[1 + \sup_{0 \leq u \leq s} |T(u)|^2 \right] ds \right).$$

Since $T_0 \in L^2(\Omega, \mathcal{F}_0, \mathbb{P})$, an application of Gronwall's inequality yields

$$\mathbb{E} \left[\sup_{0 \leq t \leq t_f} |T(t)|^2 \right] < \infty.$$

Consequently, it follows that

$$T \in L^2(\Omega; C([0, t_f])),$$

which completes the proof. $\square$

This result ensures that the stochastic thermal component of the proposed model is mathematically well posed under the established regularity conditions.

2.4.3. Explicit Representation in the Linear Case

A particularly relevant case arises when the deterministic heat-transfer term is linear in the temperature state and the diffusion coefficient is state-independent over short time intervals. Under these assumptions, the stochastic temperature equation admits an explicit analytical solution. Define

$$\alpha := \frac{\lambda A_s}{C_{\text{eff}} L}, \quad (19)$$

where α denotes the effective heat-transfer coefficient associated with the product-package system.

So that the physics-based stochastic temperature model becomes

$$dT_{\text{stochastic}}(t) = \alpha(T_{\text{amb}}(t) - T_{\text{stochastic}}(t)) dt + \sigma(t) dW(t). \quad (20)$$

This equation may be interpreted as a time-dependent Ornstein–Uhlenbeck-type model. By the variation-of-constants formula, its solution can be written as

$$T_{\text{stochastic}}(t) = e^{-\alpha t} T_0 + \int_0^t e^{-\alpha(t-s)} \alpha T_{\text{amb}}(s) ds + \int_0^t e^{-\alpha(t-s)} \sigma(s) dW(s). \quad (21)$$

Equation (21) provides a useful physical interpretation of the model. The exponential factor $e^{-\alpha(t-s)}$ describes the memory decay of the thermal system: larger values of α correspond to faster adjustment to ambient conditions, whereas smaller values of α indicate stronger insulation and slower thermal response. Consequently, this parameter governs the rate at which the product temperature relaxes toward the surrounding environment.

Once the stochastic temperature trajectory $T_{\text{stochastic}}(t)$ is obtained, the machine-learning correction introduced previously in Equation (3) can be applied to obtain the corrected prediction $T_{\text{pred}}(t)$. This preserves the physical interpretability of the underlying heat-transfer dynamics while allowing data-driven residual effects to be incorporated at the prediction stage.

2.4.4. Statistical Properties of Temperature and Quality Dynamics

For the linear stochastic temperature model introduced in Equation (20), the first two moments can be characterized explicitly. Under suitable integrability assumptions, taking expectations in Equation (21) yields

$$\mathbb{E}[T_{\text{stochastic}}(t)] = e^{-\alpha t} \mathbb{E}[T_0] + \alpha \int_0^t e^{-\alpha(t-s)} \mathbb{E}[T_{\text{amb}}(s)] ds, \quad (22)$$

where the expectation of the stochastic integral vanishes because the Itô integral has zero mean under the stated assumptions. Consequently, the expected temperature evolution

is entirely determined by the deterministic heat-transfer core and the expected ambient temperature profile.

If the diffusion coefficient is deterministic (or independent of the Wiener process), the corresponding variance satisfies

$$\text{Var}(T_{\text{stochastic}}(t)) = e^{-2\alpha t} \text{Var}(T_0) + \int_0^t e^{-2\alpha(t-s)} \sigma^2(s) ds. \quad (23)$$

Equation (23) shows that the uncertainty associated with the temperature process results from the combined effects of the initial thermal variability and the cumulative stochastic perturbations acting throughout the cold-chain operation. The exponential weighting reflects the progressive attenuation of past disturbances as the system approaches thermal equilibrium.

These expressions provide direct insight into the influence of insulation properties and stochastic forcing on thermal reliability. Specifically, the diffusion coefficient $\sigma(t)$ governs the magnitude of temperature variability, while the parameter α scales the thermal response time to changing ambient conditions.

We now consider the associated quality dynamics. Given a simulated temperature trajectory $T(t)$, the Arrhenius relation defines the degradation rate, which transforms the quality equation into an ordinary differential equation with a random coefficient.

Theorem 2 (Quality dynamics and positivity). *Assume that $T(t)$ is an adapted process satisfying Assumption A4. Then the quality equation (12), subject to the initial condition $Q(0) = 1$, admits the unique solution*

$$Q(t) = \exp\left(-\int_0^t A \exp\left(-\frac{E_a}{R T(s)}\right) ds\right). \quad (24)$$

Moreover,

$$0 < Q(t) \leq 1, \quad t \in [0, T_f], \quad a.s., \quad (25)$$

and $Q(t)$ is non-increasing in time.

Proof. By Assumption 4, the temperature remains strictly positive, so the Arrhenius degradation rate

$$k_{\text{chem}}(t) = A \exp\left(-\frac{E_a}{R T(t)}\right)$$

is finite and nonnegative for all $t \in [0, T_f]$. Consequently, the quality equation is a first-order linear ordinary differential equation with a measurable coefficient. The classical existence and uniqueness theorem for linear ordinary differential equations therefore guarantees the existence of a unique solution, which is given explicitly by Equation (24).

Since the exponent in Equation (24) is nonpositive, it follows immediately that

$$0 < Q(t) \leq 1.$$

Finally,

$$\frac{dQ(t)}{dt} = -k_{\text{chem}}(t) Q(t) \leq 0,$$

because both $k_{\text{chem}}(t)$ and $Q(t)$ are nonnegative. Therefore, $Q(t)$ is non-increasing over time, which confirms that product quality can only deteriorate throughout the storage period. $\square$

The preceding analysis establishes that the temperature process possesses consistent statistical moments and that the corresponding quality dynamics remain physically sound. Accordingly, this stochastic representation provides a mathematically rigorous model to characterize the coupled evolution of temperature and product quality under uncertainty, establishing a solid foundation for the subsequent uncertainty quantification and Monte Carlo simulations.

2.4.5. Temperature Sensitivity and Risk Metrics

The Arrhenius law demonstrates the strong sensitivity of product degradation to temperature variations. To evaluate this dependence, the degradation-rate function is written as

$$\Phi(T) = A \exp\left(-\frac{E_a}{RT}\right), \quad (26)$$

which is strictly increasing for all $T > 0$. Indeed,

$$\Phi'(T) = A \exp\left(-\frac{E_a}{RT}\right) \frac{E_a}{RT^2} > 0. \quad (27)$$

Therefore, higher temperatures necessarily produce larger degradation rates. Combined with the explicit representation of the quality index in Equation (24), this monotonicity establishes a direct link between temperature evolution and product deterioration. As a consequence, let us assume that two temperature trajectories satisfy

$$T_1(t) \leq T_2(t), \quad t \in [0, T_f],$$

then the corresponding quality trajectories satisfy

$$Q_1(t) \geq Q_2(t), \quad t \in [0, T_f]. \quad (28)$$

This comparison property follows directly from the monotonicity of the Arrhenius degradation rate and the exponential representation of the quality function. Consequently, temperature trajectories with larger thermal excursions inevitably provoke an accelerated quality loss.

The preceding result naturally motivates the definition of probabilistic safety and risk metrics. A primary thermal reliability indicator quantifies the probability of exceeding a critical temperature threshold, defined as

$$P_{\text{fail}} = \mathbb{P}\left(\sup_{t \in [0, T_f]} T(t) > T_{\text{crit}}\right), \quad (29)$$

which represents a path-dependent event rather than a pointwise exceedance. This distinction is particularly important in cold-chain systems because even brief temperature excursions may accelerate degradation. Consequently, the reliability measure defined in Equation (29) accounts for the entire thermal history experienced by the product rather than isolated measurements.

Similarly, a quality-based failure event is defined as

$$P_{\text{qual}} = \mathbb{P}\left(Q(T_f) < Q_{\min}\right), \quad (30)$$

where $Q_{\min}$ denotes the minimum acceptable quality level. Unlike the thermal criterion, this probability quantifies the risk of the product condition falling below an admissible threshold after the cumulative effects of temperature exposure have been incorporated

through the Arrhenius degradation model. Together, Equations (29) and (30) provide complementary reliability indicators that are estimated numerically through Monte Carlo simulation in the computational experiments presented in Section 4.

2.4.6. Numerical Approximation and Model Implications

For simulation purposes, the stochastic temperature process can be approximated using the Euler–Maruyama scheme. Let $\Delta t > 0$ and define $t_n = n\Delta t$. Then,

$$T_{n+1} = T_n + b(t_n, T_n, X_{t_n})\Delta t + \Sigma(t_n, T_n, X_{t_n})\Delta W_n, \quad (31)$$

where $\Delta W_n \sim \mathcal{N}(0, \Delta t)$ are independent Gaussian increments. The Euler–Maruyama approximation provides a discrete-time representation of the continuous stochastic temperature model while preserving its probabilistic structure.

Under Assumptions 2 and 3, this scheme converges strongly with order 1/2 and weakly with order 1 under standard regularity conditions. These convergence properties ensure that the numerical trajectories consistently approximate the solution of the underlying stochastic differential equation as the time step Δt decreases. Consequently, Monte Carlo estimators based on Equation (31) provide a mathematically justified approach for estimating expectations, reliability measures, and failure probabilities. Accordingly, the proposed numerical approximation constitutes the computational basis for the stochastic simulations and uncertainty quantification procedures presented in the following section.

Once a discrete temperature trajectory $\{T_n\}$ has been generated, the corresponding quality evolution may be approximated by

$$Q_{n+1} = Q_n \exp\left(-A \exp\left(-\frac{E_a}{R T_n}\right) \Delta t\right), \quad (32)$$

which preserves both positivity and the monotonic decay of the quality index. This discrete representation is fully consistent with the continuous Arrhenius degradation model and provides a computationally efficient procedure for updating product quality along each simulated temperature trajectory.

The preceding theoretical and numerical results establish that the hybrid methodology is mathematically well posed and suitable for computational analysis. The temperature process admits a unique strong Itô solution, the quality dynamics remain physically consistent, degradation exhibits a rigorous dependence on temperature through the Arrhenius law, and reliability metrics can be evaluated using probabilistic simulation. Consequently, the proposed stochastic architecture provides a rigorous foundation for uncertainty quantification, reliability assessment, and predictive analysis in temperature-sensitive cold-chain systems, while naturally supporting the computational implementation developed in the following section.

3. Numerical Example and Model Simulation

This section illustrates the application of the developed approach through a pharmaceutical cold-chain transportation case study based on realistic operating conditions. The mathematical model developed in Section 2 is applied to characterize stochastic temperature evolution, product degradation, and system reliability, demonstrating its utility for uncertainty analysis and predictive decision support.

3.1. Representative Pharmaceutical Cold-Chain Transportation Scenario

The numerical study considers a pharmaceutical cold-chain transportation scenario representative of centralized medicine distribution systems. The logistics configuration is consistent with the distribution network investigated by Pérez Lechuga [2]. Whereas

that analysis focused on logistics optimization and distribution planning, the present work addresses stochastic temperature evolution, pharmaceutical degradation, and predictive reliability during refrigerated transportation.

Among the pharmaceutical products listed in Table 2, human insulin was selected as the representative case study because of its widespread clinical use, strict cold-chain requirements, and well-documented thermal sensitivity. Although the proposed stochastic methodology is applicable to any temperature-sensitive pharmaceutical product, insulin provides an appropriate benchmark for evaluating the predictive capability of the integrated model under realistic transportation conditions.

Table 2. Representative temperature-sensitive pharmaceutical products considered in this study. Abbreviations: ST = storage temperature (°C); DM = degradation mechanism; CA = clinical application.

Product	ST	DM	CA
Human insulin	2–8	Protein denaturation	Diabetes
Influenza vaccine	2–8	Antigen degradation	Immunization
Monoclonal antibodies	2–8	Protein aggregation	Oncology/Autoimmune
Erythropoietin	2–8	Loss of biological activity	Nephrology
Human growth hormone	2–8	Protein degradation	Endocrinology

Table 3 summarizes the physical and operational parameters adopted for this pharmaceutical case study. Whenever possible, these values were obtained from published experimental studies, international guidelines, and engineering reference sources [4,20,33,34]. The remaining parameters were selected to represent realistic operating conditions or calibrated for the computational analysis, ensuring physically meaningful temperature evolution and product degradation while preserving the general applicability and reproducibility of the presented approach. The Arrhenius degradation parameters correspond to representative values commonly reported for temperature-sensitive formulations and are intended to demonstrate the proposed model rather than characterize a specific commercial formulation. Since the activation energy and frequency factor depend on the physico-chemical properties and degradation mechanisms of each pharmaceutical product, these parameters should be recalibrated when the methodology is applied to a particular drug or biological product.

Table 3. Physical, operational, and degradation-model parameters adopted for the representative insulin transportation scenario. Abbreviations: A = Assumed; B = World Health Organization (WHO); C = Representative summer conditions in central Mexico; D = Representative transportation scenario; E = Literature or model calibration; F = Representative pharmaceutical stability literature.

Parameter	Symbol	Value	Unit	Ref.
Initial product temperature	T_0	5	°C	A
Recommended storage temperature	T_{rec}	2–8	°C	B
Average ambient temperature	T_{amb}	30	°C	C
Transport duration	T_f	4	h	D
Sampling interval	Δt	1	min	A
Thermal conductivity	λ	–	$\text{W m}^{-1} \text{K}^{-1}$	E
Effective heat capacity	C_{eff}	–	J K^{-1}	E
Insulation thickness	L	–	m	E
Heat-transfer area	A_s	–	m^2	E
Diffusion coefficient	σ	–	$\text{K h}^{-1/2}$	E
Activation energy	E_a	–	kJ mol^{-1}	F
Pre-exponential factor	A	–	h^{-1}	F

3.2. Numerical Simulation Setup

The numerical study evaluates the thermal behavior, product degradation, and reliability of the representative transportation scenario using the mathematical model developed in Section 2. The stochastic differential equation is solved by the Euler–Maruyama method, and the resulting temperature trajectories are incorporated into the Arrhenius model to estimate cumulative degradation and product quality. Uncertainty is evaluated through Monte Carlo simulation by generating multiple independent temperature trajectories, from which statistical indicators, confidence intervals, and reliability metrics are obtained.

Table 4 summarizes the numerical configuration adopted in this study, including the physical model parameters, temporal discretization, Monte Carlo settings, and implementation details. These specifications define the computational setup used to evaluate the stochastic temperature dynamics and the corresponding product degradation.

Table 4. Computational configuration used for stochastic simulations and machine-learning dataset generation.

Parameter	Value	Description
Simulation time, t_f	4 h	Total transportation period
Time step, Δt	1 min (1/60 h)	Euler–Maruyama discretization step
Number of time steps	241	Temporal discretization points
Monte Carlo realizations	1000	Stochastic simulations
Initial temperature	5.0 °C	Initial product temperature
Ambient temperature	30.0 °C	External environmental temperature
Heat-transfer coefficient, α	0.015 h ^{−1}	Thermal exchange coefficient
Stochastic intensity, σ	0.120	Standard simulation value
Numerical integration	Euler–Maruyama	SDE solver
Programming language	Python 3	Numerical implementation
Computational platform	Google Colaboratory	Cloud computing environment
Random seed	2026	Reproducibility of simulations

Our approach was applied to a representative pharmaceutical cold-chain transportation case study using the operating conditions summarized in Table 3. The initial product temperature was set to $T_0 = 5$ °C and the ambient temperature to $T_{\text{amb}} = 30$ °C over a four-hour transportation period, with heat exchange modeled through an effective convection coefficient of $\alpha = 0.015$ h^{−1}. All physical and numerical parameters remained unchanged throughout the computational analysis, except for the stochastic diffusion coefficient, which was varied in the sensitivity study. The stochastic heat-transfer model was solved using the Euler–Maruyama method, and the resulting temperature trajectories were incorporated into the Arrhenius degradation model to evaluate product quality and quantify the uncertainty associated with environmental variability.

For clarity and reproducibility, the principal computational steps developed in this work are summarized in Appendix A as Algorithms A1–A4. These algorithms describe the implementation of the stochastic heat-transfer simulation, the machine-learning residual correction, the Monte Carlo uncertainty propagation, and the statistical post-processing adopted throughout the numerical study. Because the complete computational implementation is substantially more detailed than can be conveniently included in an appendix, only the core computational routines are presented. All algorithms were executed in the Google Colaboratory (Google Colab) platform [35], providing an accessible, fully reproducible, and hardware-independent workflow for the numerical experiments.

3.3. Stochastic Temperature and Quality Evolution

The developed approach was applied to evaluate the evolution of compartment temperature and pharmaceutical product quality under representative refrigerated transportation conditions.

Figure 1 presents the stochastic evolution of the transit temperature and the corresponding normalized product quality. As shown in Figure 1a, the ensemble mean temperature remains within the recommended cold-chain range throughout the delivery period, while the representative trajectories and the 95% confidence interval illustrate the variability induced by environmental disturbances. Despite these fluctuations, all predicted temperatures remain within the prescribed storage limits.

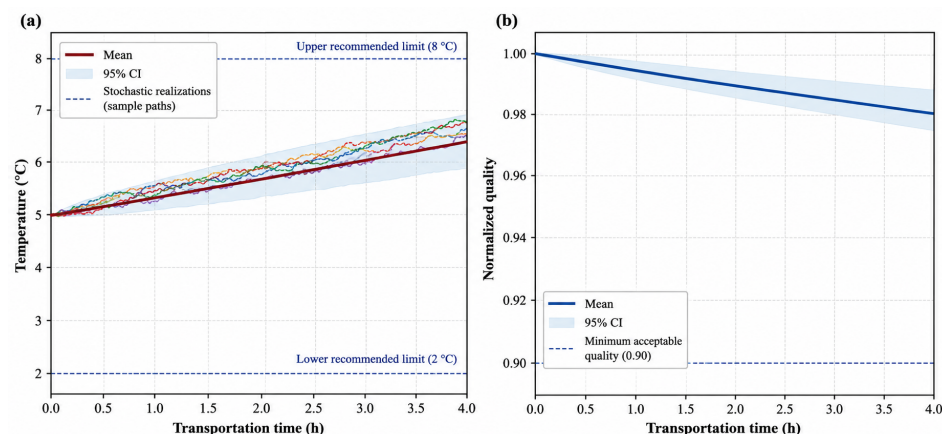


Figure 1. Stochastic evolution of transportation temperature and pharmaceutical product quality predicted by the proposed model. (a) Representative stochastic temperature trajectories obtained from the Monte Carlo simulations together with the ensemble mean and the corresponding 95% confidence interval. The dashed horizontal lines indicate the recommended cold-chain temperature limits (2–8 °C). The simulated temperature remains within the prescribed storage range throughout the transportation period despite the presence of stochastic environmental disturbances. (b) Evolution of the normalized pharmaceutical product quality computed from the Arrhenius degradation model using the simulated temperature trajectories. The ensemble mean remains well above the minimum acceptable quality threshold of 0.90 during the entire transportation period, indicating that the proposed transportation conditions preserve product integrity while maintaining a high level of thermal reliability.

The corresponding product quality evolution is shown in Figure 1b. This index decreases gradually because of cumulative thermal exposure but remains well above the minimum acceptable threshold throughout the transit schedule. The narrow confidence interval indicates that temperature uncertainty has only a limited effect on the degradation process under the operating conditions considered, demonstrating the ability of the proposed modeling approach to quantify both the expected quality evolution and the uncertainty associated with environmental variability.

3.4. Comparison Between Deterministic and Stochastic Predictions

To assess the agreement between the analytical core and the random trajectories, the ensemble statistics obtained from the Monte Carlo simulations were compared with the corresponding baseline solution, in which the stochastic diffusion term is neglected. This comparison evaluates whether the stochastic representation preserves the expected thermal behavior while providing a quantitative description of the uncertainty associated with environmental disturbances.

Figure 2 compares the nominal prediction with the ensemble statistics of the stochastic model. As shown in Figure 2a, the unperturbed temperature trajectory closely follows

the ensemble mean of the stochastic realizations throughout the transportation period. The close agreement between both predictions indicates that the stochastic structure preserves the expected average behavior. Unlike the baseline solution, however, the stochastic model additionally provides the 95% confidence interval, thereby quantifying the variability in temperature induced by environmental uncertainty.

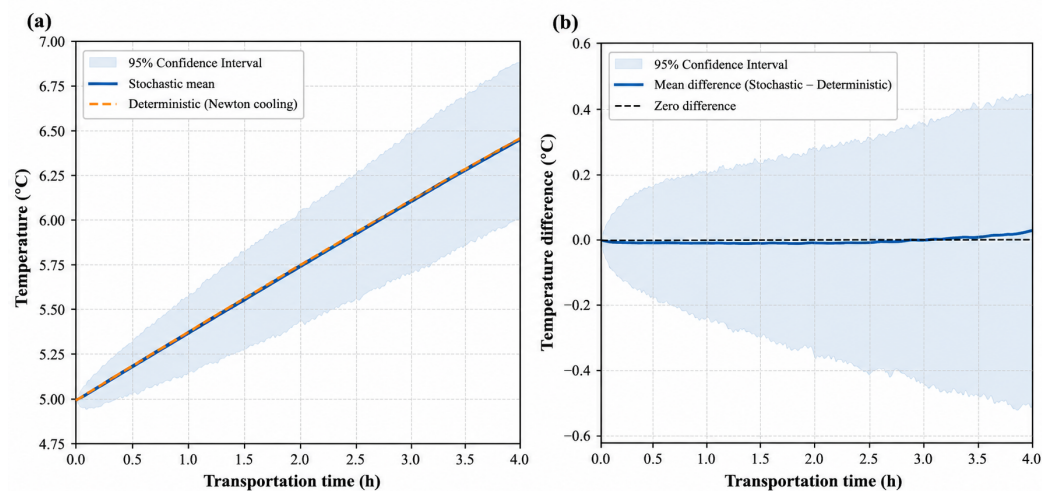


Figure 2. Comparison between the deterministic and stochastic temperature predictions. (a) Deterministic solution (dashed line), stochastic ensemble mean (solid line), and the corresponding 95% confidence interval. (b) Difference between the stochastic ensemble mean and the deterministic prediction, with the shaded region representing the 95% confidence interval and the dashed horizontal line indicating zero difference.

The corresponding difference between the stochastic ensemble mean and the nominal prediction is presented in Figure 2b. The mean difference remains close to zero throughout the transportation period, while the confidence interval reflects the variability introduced by the stochastic perturbations. The absence of systematic bias suggests that the stochastic architecture preserves the expected thermal behavior while extending the standard prediction through the explicit quantification of uncertainty.

These results suggest that the physics-informed model preserves the expected transportation dynamics while complementing the unperturbed case with probabilistic information. Such uncertainty estimates provide a more comprehensive basis for reliability assessment, risk analysis, and decision-making in pharmaceutical cold-chain management than pointwise estimates alone.

3.5. Distribution of the Final Product Quality

While the previous results describe the temporal evolution of the drug condition, the final quality at the end of transportation is of particular practical interest because it determines whether the product satisfies the required storage specifications. Accordingly, the ensemble of Monte Carlo realizations was analyzed to characterize the distribution of this terminal variable and quantify the variability associated with thermal uncertainty.

Figure 3 presents the empirical distribution of the final product quality together with the normal probability density function fitted to the simulation results. The histogram exhibits an approximately symmetric bell-shaped profile centered on the ensemble mean, indicating that the cumulative effect of thermal uncertainty introduces only limited variability in the remaining pharmaceutical integrity. The close agreement between the empirical histogram and the fitted normal curve suggests that the degradation process can be adequately characterized using conventional probabilistic measures.

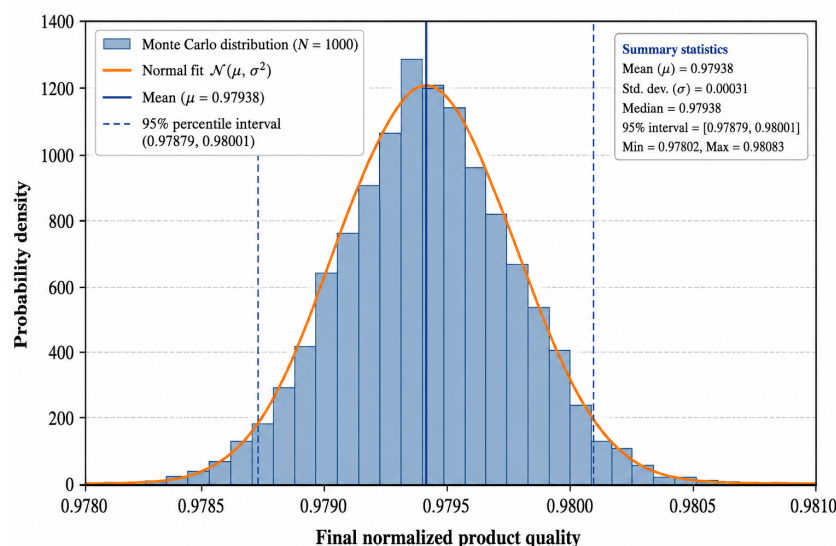


Figure 3. Distribution of the final normalized pharmaceutical product quality obtained from 1000 Monte Carlo simulations. The histogram represents the empirical probability density, while the solid curve corresponds to the fitted normal distribution. The solid vertical line indicates the mean final quality, and the dashed vertical lines denote the 95% percentile interval.

The solid vertical line denotes the mean final quality, whereas the dashed lines indicate the 95% percentile interval. The relatively narrow spread of the distribution suggests that stochastic temperature variations have only a limited influence on the cumulative degradation during the transportation period. Moreover, all simulated realizations remain well above the minimum acceptable quality threshold, supporting the reliability of the proposed transportation conditions and indicating that the products preserve an adequate safety margin throughout the distribution process.

The previous results focused on uncertainty propagation by quantifying how random environmental disturbances affect the predicted temperature and pharmaceutical integrity trajectories through Monte Carlo simulation. The following investigation addresses a different objective by evaluating the sensitivity of the model to variations in the stochastic diffusion coefficient. Whereas uncertainty analysis characterizes the probabilistic variability induced by random perturbations, sensitivity studies examine how changes in a model parameter influence the predicted response. This complementary perspective identifies the effect of the diffusion coefficient on the dispersion of the simulated temperature and remaining quality curves, providing additional insight into the robustness of the proposed stochastic methodology.

3.6. Sensitivity Analysis with Respect to the Stochastic Diffusion Coefficient

To evaluate the robustness of the presented approach, a sensitivity analysis was conducted by varying the diffusion coefficient σ , which governs the intensity of the stochastic perturbations affecting the transportation temperature. For each value of σ , 1000 Monte Carlo realizations were generated, and the corresponding terminal pharmaceutical state was evaluated using the Arrhenius degradation model.

Figure 4 summarizes the distribution of the remaining quality at the final time step for different values of the stochastic diffusion coefficient. As expected, increasing σ leads to a gradual increase in the variability of the terminal condition, as evidenced by the wider interquartile ranges and longer whiskers of the boxplots. This behavior indicates that stronger environmental disturbances broaden the range of possible degradation outcomes, thereby increasing the uncertainty associated with the transportation process.

Despite this increase in spread, the median product quality remains nearly constant for all values of σ , and the predicted quality remains well above the minimum acceptable threshold across all stochastic trajectories. These results suggest that the expected degradation is only weakly influenced by moderate changes in the stochastic intensity, whereas the principal effect of increasing σ is to enlarge the uncertainty surrounding the final quality rather than to substantially modify its expected value.

Overall, the sensitivity analysis suggests that the developed model is robust under realistic levels of environmental uncertainty. Moreover, it highlights the value of explicitly incorporating stochastic perturbations to quantify the variability of product quality, thereby providing a stronger basis for reliability assessment, risk analysis, and decision-making in pharmaceutical cold-chain transportation.

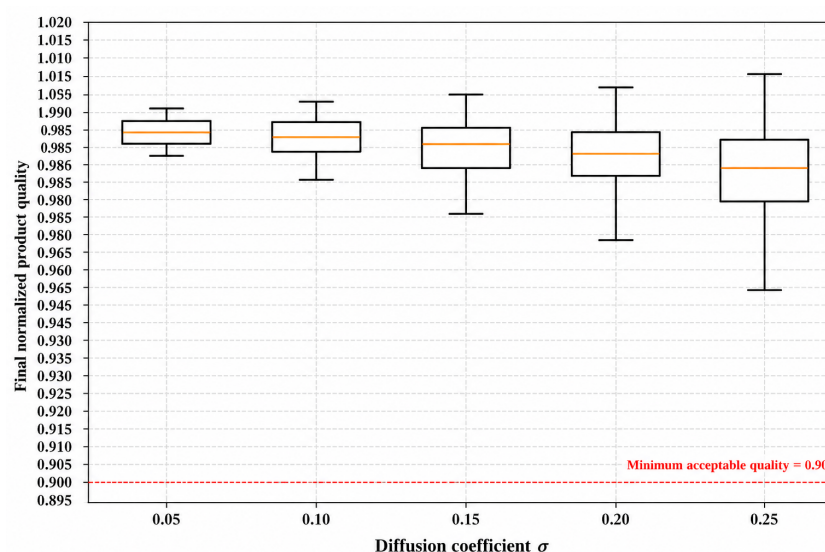


Figure 4. Sensitivity analysis of the stochastic diffusion coefficient σ . Boxplots of the final normalized pharmaceutical product quality obtained from 1000 Monte Carlo simulations for different values of σ . As the diffusion coefficient increases, the variability of the final product quality becomes progressively larger, while the median quality remains well above the minimum acceptable threshold, indicating that the proposed transportation conditions are robust against increasing environmental uncertainty.

3.7. Propagation of Uncertainty During Transportation

One of the main advantages of the proposed method is its ability to characterize not only the expected thermal behavior but also the propagation of variance throughout the transit process. Because environmental disturbances accumulate over time, analyzing the evolution of probabilistic spread provides additional insight into the reliability and robustness of the cold chain beyond that obtained from the ensemble mean alone.

Figure 5 illustrates the propagation of uncertainty in both the compartment temperature and the corresponding product quality. As shown in Figure 5a, the standard deviation of the thermal field increases progressively over time, indicating that random environmental perturbations accumulate as the stochastic process evolves. This behavior is characteristic of stochastic heat-transfer systems, where variability naturally grows under the continuous influence of external disturbances.

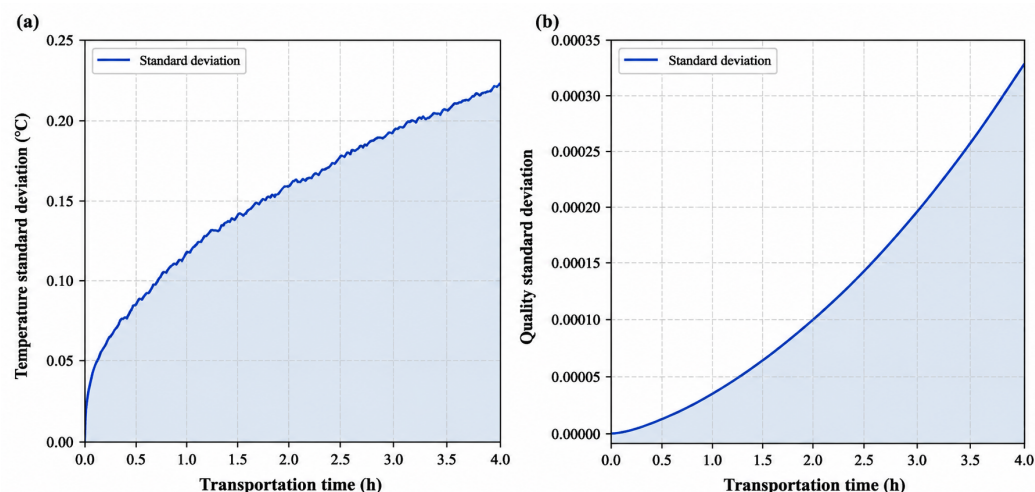


Figure 5. Propagation of uncertainty during refrigerated transportation. (a) Temporal evolution of the standard deviation of the product temperature obtained from the Monte Carlo simulations, illustrating the progressive accumulation of thermal uncertainty. (b) Temporal evolution of the standard deviation of the normalized pharmaceutical product quality. Although temperature uncertainty increases throughout transportation, the uncertainty propagated to product quality remains comparatively small, demonstrating the robustness of the proposed transportation conditions.

The corresponding uncertainty in product quality is presented in Figure 5b. Although the thermal variance expands throughout the transit period, the variability propagated to the degradation process remains comparatively small. The standard deviation of the normalized integrity index exhibits only a modest increase, suggesting that the cumulative degradation process naturally attenuates the effect of short-term thermal fluctuations. Consequently, random temperature variations produce only limited variability in the final pharmaceutical status under the representative operating conditions considered.

These results reveal an important characteristic of the proposed probabilistic structure. While uncertainty continuously develops in the thermal dynamics, only a fraction of it is transferred to the degradation process. This behavior suggests that the refrigerated transportation conditions are robust and that the developed computational architecture not only predicts the expected system response but also quantifies the propagation of probabilistic spread, providing valuable information for reliability evaluation, risk assessment, and decision-making in pharmaceutical cold-chain management.

4. Machine-Learning-Based Residual Correction

Although the stochastic heat-transfer model captures the dominant mechanisms governing temperature evolution during refrigerated transportation, practical cold-chain operations are influenced by additional factors that are difficult to represent analytically. Local airflow patterns, heterogeneous insulation properties, loading conditions, sensor inaccuracies, and other operational effects may introduce systematic discrepancies between the numerical estimates and the observed temperature. Consequently, residual prediction deviations may remain even after the physical and stochastic components have been taken into account.

To reduce these discrepancies, a machine-learning (ML) residual correction is incorporated. Rather than replacing the underlying physical model, the ML component learns the remaining systematic prediction error from observational data and provides a corrective term to the stochastic temperature prediction. This hybrid architecture preserves the physical interpretability of the governing equations while improving predictive accuracy by accounting for effects that are not explicitly represented in the mathematical core.

Let

$$r(t) = T_{\text{obs}}(t) - T_{\text{physics}}(t),$$

denote the residual error between the observed product temperature and the prediction generated by the physics-based stochastic model. The objective of the machine-learning algorithm is to approximate the nonlinear mapping

$$f_{\text{ML}} : X_t \longrightarrow r(t),$$

where X_t denotes the feature vector containing the variables that influence the thermal behavior during transportation. Representative input variables include the predicted product temperature, ambient temperature, transportation time, accumulated thermal exposure, the stochastic diffusion coefficient, and other operational metrics when available.

Once trained, the estimated residual correction is incorporated into the stochastic heat-transfer model through the additive correction

$$dT = \alpha(T_{\text{amb}} - T) dt + f_{\text{ML}}(X_t) dt + \sigma dW_t,$$

where the first term describes the deterministic heat-transfer dynamics, the second term represents the machine-learning residual correction, and the third term accounts for stochastic environmental perturbations through a Wiener process.

The data-driven model is trained using supervised learning by minimizing the discrepancy between the predicted residual and the observed counterpart over a representative collection of transportation records. Subsequently, the learned correction is incorporated into every Monte Carlo realization, allowing the stochastic simulations to simultaneously account for the governing physical mechanisms, random environmental uncertainty, and systematic prediction errors inferred from historical transit data. This hybrid modeling architecture improves predictive accuracy while preserving the physical consistency and interpretability of the underlying mathematical core.

The machine-learning dataset was generated directly from the stochastic Monte Carlo simulations of the proposed heat-transfer model. A total of 1000 independent temperature trajectories were simulated over a representative 4 h transportation period using a sampling interval of one minute, yielding 241 temporal observations per realization and a total of 241,000 samples. Each sample consisted of five input features, namely the predicted product temperature, ambient temperature, transportation time, accumulated thermal exposure, and stochastic diffusion coefficient, while the target variable corresponded to the residual temperature error defined as the difference between the observed (reference) temperature and the prediction obtained from the physics-based stochastic model. The resulting matrix was partitioned into 80% training and 20% testing subsets using the GroupShuffleSplit mechanism to ensure that all observations belonging to the same simulated path remained within a single subset, thereby preventing information leakage. A fixed random seed (2026) was employed to guarantee reproducibility of the computational experiments. Since the data was entirely generated by numerical simulation, no missing values were present, and no feature normalization or scaling was required prior to training because the selected Gradient Boosting algorithm is insensitive to the magnitude of the predictor variables. Residuals were computed after completing each stochastic simulation and before the partitioning step, ensuring that the learning algorithm was trained exclusively on the residual prediction error associated with the physics-based model.

4.1. Training and Validation of the Machine Learning Model

The machine-learning component was developed to estimate the residual deviation between the physics-based stochastic model and the observed transit temperatures, pro-

viding a data-driven correction while preserving the governing heat-transfer and degradation equations.

The dataset generated from the stochastic simulations was divided into training (80%) and testing (20%) subsets, and five supervised regression algorithms were evaluated for residual correction using the coefficient of determination (R^2), the root mean square error (RMSE), and the mean absolute error (MAE). The selected architecture accurately reproduced the residuals while maintaining consistent performance on both partitions, indicating good generalization. The trained predictor was subsequently incorporated into the stochastic heat-transfer core through the correction term $f_{ML}(X_t)$. Tables 5 and 6 summarize the comparative performance of the evaluated approaches and their robustness under different noise levels.

Table 5. Comparative performance of different machine learning models for residual correction.

Model	R^2	RMSE (°C)	MAE (°C)	Training Time (s)
Polynomial Regression	0.9364	0.002034	0.001623	0.10
Gradient Boosting	0.9284	0.002158	0.001721	36.53
Random Forest	0.9282	0.002161	0.001714	139.54
Linear Regression	0.8392	0.003233	0.002562	0.02
MLP Neural Network	0.2089	0.007172	0.006563	6.51

Note: The best performance achieved for each evaluation metric is highlighted in bold.

As illustrated in Figure 6, the testing samples are densely distributed around the ideal prediction line, indicating that the regression model accurately reproduces the residual thermal behavior over the entire range of observations. Although a moderate dispersion is observed due to the stochastic nature of the residuals, no significant systematic bias is evident. The close agreement between the training and testing coefficients of determination ($R^2_{\text{train}} = 0.932$ and $R^2_{\text{test}} = 0.928$), together with the low prediction errors (RMSE = 0.0022 °C and MAE = 0.0017 °C), demonstrates that the model generalizes well to previously unseen data. These results confirm that the machine-learning component effectively captures the systematic discrepancies not represented by the physics-based heat-transfer model, thereby improving the accuracy of the hybrid stochastic framework used for subsequent temperature prediction and pharmaceutical quality assessment.

Table 6. Performance stability of the evaluated models under different noise levels.

Scenario	Model	R^2	RMSE	MAE	Reduction (%)
Low Noise	MLP Neural Network	0.9836	0.0010	0.0008	94.47
	Polynomial Regression	0.9823	0.0010	0.0008	94.25
	Random Forest	0.9769	0.0012	0.0009	93.43
	Gradient Boosting	0.9746	0.0013	0.0010	93.11
	Linear Regression	0.8810	0.0027	0.0022	85.09
Medium Noise	MLP Neural Network	0.9374	0.0020	0.0016	88.96
	Polynomial Regression	0.9366	0.0020	0.0016	88.89
	Random Forest	0.9294	0.0021	0.0017	88.28
	Gradient Boosting	0.9291	0.0021	0.0017	88.25
	Linear Regression	0.8406	0.0032	0.0026	82.38
High Noise	MLP Neural Network	0.7879	0.0040	0.0032	78.25
	Polynomial Regression	0.7879	0.0040	0.0032	78.25
	Gradient Boosting	0.7813	0.0041	0.0033	77.92
	Random Forest	0.7748	0.0042	0.0033	77.59
	Linear Regression	0.7062	0.0048	0.0038	74.41

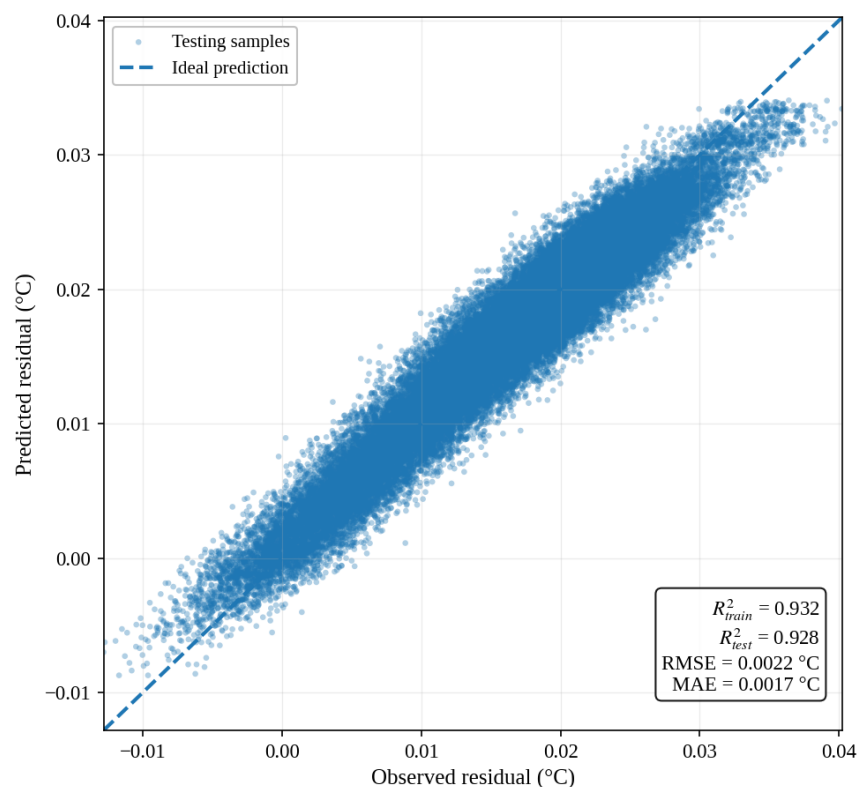


Figure 6. Validation of the machine-learning residual correction model. Predicted residuals are compared with the observed residuals for the independent testing dataset. The dashed line represents the ideal one-to-one prediction. The high concentration of samples around the diagonal and the obtained performance metrics ($R^2_{train} = 0.932$, $R^2_{test} = 0.928$, RMSE = 0.0022 °C, and MAE = 0.0017 °C) demonstrate that the proposed model accurately captures the residual temperature errors and provides reliable corrections to the physics-based stochastic model.

4.2. Interpretation of Feature Importance

Following the comparative evaluation of the machine-learning algorithms, the relative importance of the input features was analyzed to provide a physical interpretation of the selected architecture. Feature importance analysis identifies the variables that contribute most to the residual correction and offers additional insight into the interaction between the data-driven and physics-informed components of the proposed hybrid methodology.

Figure 7 presents the relative importance of the input predictors estimated by the Gradient Boosting regression model. Thermal exposure and transportation time are the two dominant inputs, together accounting for more than 60% of the total weight. This result is consistent with the cumulative nature of heat transfer and pharmaceutical degradation, since both variables characterize the progressive thermal load experienced by the product throughout transportation.

Ambient temperature also exhibits a substantial impact, indicating that external environmental conditions influence the residual thermal behavior not fully represented by the analytical heat-transfer model. In contrast, product temperature contributes a smaller but still meaningful proportion of the overall predictive weight, providing complementary information for estimating the residual correction.

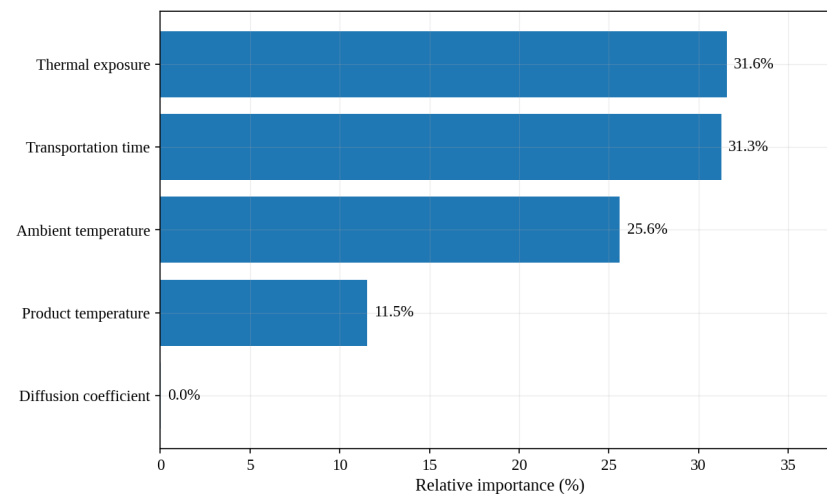


Figure 7. Relative importance of the input features used by the Gradient Boosting regression model to estimate the residual correction. The bars indicate the normalized contribution of each feature to the prediction process. Thermal exposure and transportation time constitute the dominant predictors, followed by ambient temperature and product temperature, whereas the diffusion coefficient exhibits a negligible contribution under the simulated operating conditions.

The diffusion coefficient exhibits a negligible effect under the representative operating conditions considered, indicating that the residual correction is driven primarily by the accumulated thermal history rather than by the magnitude of the stochastic perturbations. Overall, the feature importance analysis shows that the selected machine-learning model captures physically meaningful relationships. It should be noted, however, that these metrics quantify the relative predictive contribution of each variable and should not be interpreted as measures of causality or physical sensitivity.

Table 7 summarizes the principal quantitative indicators obtained from the proposed hybrid methodology. The results indicate that the refrigerated transportation system maintained the product within the recommended thermal conditions, preserving pharmaceutical quality while achieving high predictive accuracy through the machine-learning residual correction. Collectively, these indicators demonstrate the effectiveness of the proposed framework for temperature prediction, product quality assessment, and uncertainty quantification in pharmaceutical cold-chain transportation.

Table 7. Summary of the key performance indicators obtained from the proposed hybrid methodology.

Category	Performance Indicator	Value
Thermal Performance	Mean product temperature	5.00 °C
	Temperature excursion probability	0.001
	Reliability index	1.000
Product Quality	Expected final quality	0.9879
	Standard deviation of final quality	0.00048
	Probability of quality failure	0.000
Machine Learning	Training R^2	0.932
	Testing R^2	0.928
	Testing RMSE	0.00216 °C
	Testing MAE	0.00172 °C

4.3. Extension to Multiple Pharmaceutical Products

The methodology presented in this work considers the transportation of a single pharmaceutical product to clarify the integration of stochastic heat transfer, degradation

kinetics, and machine-learning residual correction. However, the proposed formulation can be naturally extended to refrigerated shipments containing multiple compounds with different thermal properties, degradation kinetics, and storage requirements.

Assume that a refrigerated container transports N pharmaceutical products. Let $T_i(t)$ denote the temperature of product i , where $i = 1, \dots, N$. Because individual products may differ in packaging geometry, thermal inertia, insulation characteristics, degradation parameters, and spatial location within the refrigerated container, each item is described by its own stochastic heat-transfer equation:

$$dT_i = \alpha_i(T_{\text{amb}} - T_i)dt + f_{\text{ML},i}(X_i)dt + \sigma_i dW_i(t), \quad i = 1, \dots, N,$$

where the parameters α_i , σ_i , and the machine-learning correction $f_{\text{ML},i}(X_i)$ may differ from one item to another according to their individual thermal properties and transportation conditions.

The corresponding degradation process is obtained by assigning product-specific Arrhenius parameters and quality equations to each formulation. Consequently, the proposed methodology can simultaneously predict the thermal evolution, degradation, and remaining quality of heterogeneous pharmaceutical shipments while preserving the physical interpretation of the underlying stochastic model. This extension provides a natural basis for analyzing mixed refrigerated transportation, where products with different stability requirements are exposed to the same environmental conditions but exhibit distinct thermal responses and degradation rates.

Similarly, the degradation of each pharmaceutical product is evaluated through its corresponding Arrhenius model,

$$Q_i(t) = Q_{i,0} \exp\left(-\int_0^t k_i(T_i(s)) ds\right),$$

where the degradation kinetics are compound-specific through the corresponding activation energies, pre-exponential factors, and initial quality conditions. This representation allows each formulation to respond differently to the same thermal environment according to its intrinsic physicochemical properties.

The overall transportation performance can then be characterized through aggregate quality indicators. For example, the mean product quality is defined as

$$\bar{Q}(t) = \frac{1}{N} \sum_{i=1}^N Q_i(t),$$

whereas the minimum quality,

$$Q_{\min}(t) = \min_{1 \leq i \leq N} Q_i(t),$$

provides a conservative performance indicator by identifying the most thermally affected item within the shipment. Such indicators are particularly useful for verifying compliance with cold-chain quality requirements when multiple drugs are transported simultaneously.

From a computational perspective, the proposed methodology naturally extends to heterogeneous shipments by propagating the stochastic temperature trajectory and the corresponding degradation process for each item. Because the temperature and quality evolution of each compound are evaluated independently once the transportation conditions have been specified, the calculations can be performed in parallel. Consequently, the computational cost grows approximately linearly with the number of transported units, making this approach suitable for large-scale pharmaceutical distribution systems.

This generalized framework preserves the mathematical structure of the proposed stochastic model while extending its applicability to realistic refrigerated transportation involving heterogeneous pharmaceutical shipments. It therefore provides a unified approach for evaluating product-specific quality evolution, shipment-level reliability, and operational risk without requiring fundamental modifications to the underlying mathematical core.

4.4. Computational Complexity and Scalability Analysis

From a computational perspective, the proposed methodology consists of four principal steps: (i) numerical integration of the stochastic heat-transfer equation using the Euler–Maruyama scheme, (ii) evaluation of the Arrhenius degradation model, (iii) machine-learning residual correction, and (iv) Monte Carlo uncertainty propagation followed by statistical post-processing. Since these routines are executed sequentially for each stochastic temperature realization, the overall computational complexity can be analyzed by examining the cost of each element separately.

Let N_t denote the number of temporal discretization points, M the number of Monte Carlo realizations, and N_p the number of pharmaceutical products transported simultaneously. For a single stochastic trajectory, the Euler–Maruyama integration requires one update per time step, resulting in a computational cost of order $\mathcal{O}(N_t)$. The Arrhenius degradation model and the machine-learning residual correction are both evaluated once per time step and therefore preserve this linear behavior. Consequently, the computational cost associated with a single realization remains proportional to the time-step count.

Proposition 1 (Computational Complexity). *Let N_t be the number of time discretization points, M the number of Monte Carlo realizations, and N_p the number of transported pharmaceutical products. Assuming that the evaluation of the machine-learning residual correction requires bounded computational effort per time step, the overall computational complexity of the proposed hybrid stochastic methodology satisfies*

$$C(N_p, M, N_t) = \mathcal{O}(N_p M N_t).$$

Proof. Each stochastic realization requires $\mathcal{O}(N_t)$ operations for the numerical integration of the stochastic heat-transfer equation. The Arrhenius degradation model and the machine-learning residual correction are evaluated once per time step and therefore contribute only linear complexity with respect to N_t . Repeating this procedure for M Monte Carlo realizations yields a computational cost of $\mathcal{O}(M N_t)$ for a single formulation. Finally, extending the methodology to N_p independent compounds increases the processing effort linearly, leading to the overall complexity

$$\mathcal{O}(N_p M N_t).$$

□

An important computational characteristic of the proposed approach is that the Monte Carlo realizations are mutually independent once the environmental conditions have been specified. Likewise, the stochastic evolution of different pharmaceutical products can be computed independently in the generalized multi-product framework. Consequently, both the Monte Carlo simulations and the product-specific degradation calculations are naturally parallelizable. If P processing units are available, the expected execution time may be approximated by

$$T_P \approx \frac{T_1}{P} + T_{\text{sync}},$$

where T_1 denotes the execution time using a single core and T_{sync} represents the synchronization overhead, which is typically small compared with the overall computational cost. This property makes the presented routines particularly suitable for implementation on modern multi-core architectures, cloud computing platforms, and distributed high-performance computing environments.

The complete numerical workflow was implemented in Python using a modular architecture consisting of independent routines for stochastic integration, degradation evaluation, machine-learning residual correction, uncertainty propagation, and statistical post-processing. This modular implementation facilitates reproducibility and enables straightforward incorporation of additional degradation mechanisms, alternative learning algorithms, or parallel computing strategies without modifying the underlying mathematical core.

Overall, the proposed methodology exhibits linear computational complexity with respect to the principal problem dimensions and naturally supports parallel execution. These characteristics make it computationally scalable and suitable for uncertainty quantification and reliability assessment in large-scale pharmaceutical cold-chain transportation systems involving numerous products, extended transportation horizons, and a large number of Monte Carlo realizations.

5. Results and Discussion

The results obtained throughout the numerical study demonstrate that the proposed numerical workflow provides a physically consistent representation of temperature evolution and pharmaceutical product degradation under uncertain transportation conditions. The comparison between the deterministic and probabilistic structures shows that the stochastic model preserves the expected thermal behavior while providing additional statistical information that cannot be obtained from deterministic predictions alone. In particular, the close agreement between the deterministic solution and the ensemble mean indicates that the stochastic architecture introduces uncertainty without introducing systematic bias into the temperature estimates.

These findings are consistent with previous studies on pharmaceutical cold-chain monitoring, where deterministic heat-transfer models have been shown to provide reliable estimates of the average thermal behavior but are unable to quantify the uncertainty associated with environmental disturbances and operational variability. By incorporating stochastic dynamics together with a physics-informed machine-learning residual correction, the proposed framework extends these approaches by providing both accurate temperature modeling and probabilistic estimates of chemical deterioration, thereby offering a more comprehensive tool for quantitative risk assessment and decision support.

An important finding is that the uncertainty generated by the stochastic temperature dynamics propagates only partially to the degradation process. Although the dispersion of the temperature trajectories increases progressively during transportation, the corresponding variability in product quality remains comparatively small, and the final quality stays well above the minimum acceptable threshold under the representative operating conditions considered in this study. The sensitivity analysis further supports this observation by showing that increasing the diffusion coefficient mainly enlarges the uncertainty associated with the final quality while producing only minor changes in its expected value. These results indicate that the proposed approach is robust with respect to moderate stochastic disturbances and provides reliable estimates of the drug condition under realistic transportation conditions, making it suitable for quantitative quality risk assessment in pharmaceutical cold-chain operations.

The machine-learning residual correction complements the stochastic heat-transfer model by reducing systematic prediction errors that cannot be explicitly represented by the governing equations. The high predictive accuracy obtained during validation, together with the feature importance analysis, suggests that the learned correction is primarily governed by physically meaningful variables, including accumulated thermal exposure, transportation time, and ambient temperature. This behavior reinforces the consistency between the data-driven component and the underlying physical dynamics.

It should be noted that the feature importance obtained from the Gradient Boosting model reflects the relative predictive contribution of each input variable and should not be interpreted as evidence of causal influence or physical sensitivity. In contrast, the sensitivity analysis evaluates the response of the underlying physical model to controlled variations in the diffusion coefficient. Therefore, both analyses provide complementary but conceptually different information regarding the performance and interpretation of the proposed approach.

The hybrid architecture provides additional insights for operational planning beyond conventional fixed temperature thresholds. Instead of relying solely on whether the temperature exceeds the recommended limits, the mathematical model estimates the corresponding product quality under uncertainty by combining stochastic temperature prediction with the Arrhenius degradation model. This data enables decision makers to distinguish temporary thermal excursions that have negligible impact on pharmaceutical integrity from events that may compromise the drug status. Consequently, this framework supports more informed quality risk assessment and provides a computational basis for future decision-support systems and digital twins for pharmaceutical cold-chain management.

Our approach is particularly suitable for pharmaceutical transportation scenarios in which product degradation is governed by temperature-dependent kinetic models and uncertainty arises from environmental fluctuations during transit. Although the present study focuses on a representative cold-chain application, the mathematical structure can be readily adapted to other temperature-sensitive products, provided that the corresponding degradation kinetics and thermal parameters are appropriately calibrated.

Despite the encouraging results, several limitations should be acknowledged. The computational experiments were conducted under representative transportation conditions using literature-based degradation parameters, while the machine-learning residual correction was developed and validated using the available dataset. Consequently, additional testing using larger experimental transit data, different pharmaceutical formulations, and diverse logistic scenarios is required before large-scale industrial implementation. Future research will therefore focus on extensive empirical validation, heterogeneous packaging configurations, multi-product transportation scenarios, and adaptive machine-learning strategies capable of updating the residual correction in real time as new operational metrics become available.

The results obtained in this study suggest that cumulative thermal exposure plays an important role in determining pharmaceutical integrity. Although the classical Arrhenius equation provides an effective description of temperature-dependent degradation, these findings indicate that future developments could account for the complete thermal history experienced during distribution. One possible extension is to represent the degradation process through an integro-differential model of the form:

$$\frac{dQ(t)}{dt} = -Q(t) \left[A \exp\left(-\frac{E_a}{RT(t)}\right) + \int_0^t K(t-s) \Psi(T(s), X_s) ds \right], \quad Q(0) = Q_0, \quad (33)$$

where the Arrhenius term represents the instantaneous degradation kinetics, while the integral operator introduces a memory effect that accounts for cumulative thermal exposure

and additional operational variables. A convenient choice for this exponentially decaying kernel is given by:

$$K(t-s) = \kappa \exp[-\gamma(t-s)], \quad \kappa, \gamma > 0, \quad (34)$$

which controls both the intensity and persistence of past thermal events. When $\kappa = 0$, the integro-differential structure reduces to the classical Arrhenius equation, ensuring backward compatibility with conventional chemical kinetics.

This extended representation constitutes a possible direction for future research rather than part of the computational workflow developed in the present work. Its mathematical analysis, parameter estimation, and experimental validation remain to be investigated before it can be considered for practical applications.

6. Conclusions

This work presented a hybrid physics-informed stochastic framework for predicting temperature evolution and pharmaceutical product degradation during refrigerated transportation. The proposed approach integrates deterministic heat-transfer modeling, stochastic differential equations, Arrhenius degradation kinetics, machine-learning residual correction, and Monte Carlo simulations to provide both accurate temperature modeling and quantitative uncertainty assessment.

The computational results demonstrated that the stochastic architecture preserves the nominal thermal behavior while enriching the analysis through probabilistic characterization of temperature and product quality. Although uncertainty increases during transportation, its effect on the degradation process remains limited under the representative operating conditions considered in this study, indicating the robustness of the proposed numerical workflow.

The incorporation of the machine-learning residual correction further improved predictive accuracy by compensating for systematic discrepancies not explicitly captured by the governing physical equations. Together, the first-principles and data-driven components provide a consistent tool for supporting quality risk assessment and operational planning in pharmaceutical cold-chain management. The developed computational strategy is efficient, readily scalable to multiple pharmaceutical products, and directly applicable to intelligent cold-chain monitoring systems [36]. This capability also provides a solid foundation for future digital twins and intelligent monitoring platforms. The present study is subject to several limitations, including the use of representative transportation conditions and literature-based degradation parameters. Consequently, additional empirical testing using different pharmaceutical products, transit scenarios, and heterogeneous packaging configurations is required before large-scale industrial implementation.

Future research will focus on extending the proposed numerical workflow through adaptive machine-learning strategies, larger experimental datasets, and generalized degradation models incorporating thermal-memory effects. These developments may contribute to a new generation of predictive architectures that integrate stochastic analysis, thermodynamics, and machine learning for the design and optimization of resilient pharmaceutical cold-chain systems.

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Appendix A. Computational Algorithms

Appendix A.1. Computational Reproducibility

The computational experiments were performed under fixed and reproducible settings. Unless otherwise stated, all simulations used a pseudo-random seed of 2026, a time step of 1 min, a transportation period of 4 h, and 1000 Monte Carlo realizations. The machine-learning residual correction was implemented using the Gradient Boosting Regressor described in Section 4, and all computations were carried out in Python using the Google Colaboratory platform. The algorithms presented below summarize the numerical workflow adopted to obtain the reported results.

Algorithm A1 Hybrid Stochastic Heat-Transfer Simulation

Require: Initial product temperature T_0 , ambient temperature T_{amb} , heat-transfer coefficient α , diffusion coefficient σ , time step Δt , transportation time T_f , trained machine learning model $f_{\text{ML}}(X)$, random seed = 2026.

Ensure: Stochastic temperature trajectory $\{T_k\}_{k=0}^N$.

- 1: Set the pseudo-random number generator using seed = 2026
- 2: Compute the number of time steps: $N \leftarrow T_f / \Delta t$
- 3: Initialize T_0
- 4: **for** $k = 0, \dots, N - 1$ **do**
- 5: Generate Brownian increment $\Delta W_k \sim \mathcal{N}(0, \Delta t)$
- 6: Evaluate the machine learning residual correction $f_{\text{ML}}(X_k)$
- 7: Update the temperature

$$T_{k+1} = T_k + \alpha(T_{\text{amb}} - T_k)\Delta t + f_{\text{ML}}(X_k)\Delta t + \sigma\Delta W_k$$

8: **end for**

9: **return** $\{T_k\}_{k=0}^N$

Algorithm A2 Machine Learning Residual Correction

Require: Temperature trajectories $\{T(t)\}$, ambient conditions, transportation time, thermal exposure, diffusion coefficient, observed temperatures, random seed = 2026.

Ensure: Trained machine learning correction model $f_{\text{ML}}(X)$.

- 1: Set the pseudo-random number generator using seed = 2026
- 2: Construct the feature vector

$$X = [T, T_{\text{amb}}, t, E, \sigma]$$

- 3: Compute the residual target values

$$r = T_{\text{obs}} - T_{\text{physics}}$$

- 4: Split the dataset into training (80%) and testing (20%) subsets using a fixed random state (2026)
 - 5: Train the Gradient Boosting regression model using the training dataset
 - 6: Predict the residual correction for the testing dataset
 - 7: Compute the validation metrics: R^2 , RMSE, and MAE
 - 8: Estimate the predictive feature importance of the input variables
 - 9: Return the trained residual correction model $f_{\text{ML}}(X)$
-

Algorithm A3 Monte Carlo Temperature and Product Quality Simulation

Require: Hybrid stochastic heat-transfer model (Algorithm A1), trained machine learning correction model $f_{ML}(X)$, Arrhenius degradation model, number of Monte Carlo simulations N_{MC} , random seed = 2026.

Ensure: Temperature ensemble $\{T_i(t)\}$, quality ensemble $\{Q_i(t)\}$, and ensemble statistical indicators.

- 1: Initialize the pseudo-random number generator using seed = 2026
- 2: **for** $i = 1, \dots, N_{MC}$ **do**
- 3: Generate one stochastic temperature trajectory using Algorithm A1
- 4: Apply the machine learning residual correction $f_{ML}(X)$
- 5: Compute the corresponding pharmaceutical product quality by integrating the Arrhenius degradation model
- 6: Store the temperature trajectory $\{T_i(t)\}$
- 7: Store the quality trajectory $\{Q_i(t)\}$
- 8: **end for**
- 9: Compute the ensemble mean of the temperature trajectories
- 10: Compute the ensemble mean of the quality trajectories
- 11: Estimate the standard deviations and the corresponding 95% confidence intervals
- 12: Store the complete Monte Carlo ensemble for subsequent statistical analysis and visualization

Algorithm A4 Statistical Analysis and Visualization

Require: Monte Carlo temperature trajectories $\{T_i(t)\}$, quality trajectories $\{Q_i(t)\}$, machine learning prediction results, simulation parameters.

Ensure: Statistical indicators, validation metrics, graphical outputs, and summary tables.

- 1: Compute the ensemble mean of the temperature trajectories
- 2: Compute the ensemble mean of the quality trajectories
- 3: Estimate the standard deviations and the corresponding 95% confidence intervals
- 4: Analyze the distribution of the final product quality
- 5: Perform the sensitivity analysis with respect to the diffusion coefficient
- 6: Compute the machine learning validation metrics (R^2 , RMSE, and MAE)
- 7: Estimate the predictive feature importance of the input variables
- 8: Generate Figures 1–7 and the corresponding summary table
- 9: Export all numerical results, statistical indicators, and graphical outputs for reproducibility

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