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ARTICLE

Dynamics of Kawasaki Disease Pathogenesis under Stochastic Perturbations and Time-Delay Effects

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ABSTRACT: Kawasaki disease (KD) is an acute, self-limited pediatric vasculitis of unknown etiology and is one of the leading causes of acquired coronary artery complications in children. Endothelial dysfunction, vascular endothelial growth factor (VEGF) activity, adhesion molecule/chemokine activation, and inflammatory cytokine responses play important roles in its pathogenesis. This paper presents a delay differential equation model with stochastic perturbations to study lesion-level inflammatory mechanisms involved in Kawasaki disease pathogenesis. The model describes interactions among healthy endothelial cells, vascular endothelial growth factor (VEGF), adhesion molecules/chemokines, and inflammatory cytokine activity. Mathematically, endothelial-cell injury promotes VEGF production, VEGF contributes to adhesion molecule and chemokine activation, and the combined adhesion molecule/chemokine activity stimulates inflammatory cytokine production after a time delay. The variables are interpreted as aggregated biological activities, not as individual molecular species. The model is not designed to represent the acute, subacute, and convalescent clinical phases of Kawasaki disease separately, and coronary artery inflammation is not included as an independent state variable. Instead, endothelial dysfunction and inflammatory cytokine activity are used as indirect mechanistic indicators of vascular inflammatory progression. The model is shown to preserve positivity and boundedness under suitable dissipativity assumptions. Equilibrium points and an inflammatory feedback threshold quantity are discussed, and local stability is analyzed through the characteristic equations of the delayed system. Reported incidence data from 2020–2025 are used only as qualitative motivation for considering variability and delayed biological responses. A stochastic extension is then formulated to represent random biological and environmental fluctuations, and a stochastic nonstandard finite difference scheme is proposed to preserve positivity and boundedness in numerical simulations. The results provide a mathematical framework for studying delayed stochastic inflammatory interactions in Kawasaki disease, while highlighting that explicit modeling of clinical phases and coronary artery involvement remains an important direction for future work.

KEYWORDS: Kawasaki disease; stochastic delay differential equations; inflammatory feedback threshold; stability analysis; NSFD scheme; real data analysis; graphical analysis

1 Introduction

Kawasaki disease is an acute systemic vasculitis that predominantly occurs in young children, and may result in complications of the coronary arteries if not diagnosed and treated early. Early clinical research

identified fever, mucocutaneous manifestations, lymphadenopathy and coronary artery lesions as the primary characteristics of Kawasaki disease [1]. Subsequent epidemiological studies revealed that Kawasaki disease is highly age, seasonal and geographically biased, with the greatest disease burden in East Asia [2]. A number of studies have suggested that Kawasaki disease is triggered by infectious or environmental factors in genetically predisposed individuals. While a specific pathogen has not been identified, viral, bacterial and immune mechanisms have been frequently proposed [3]. Immunological research also suggests cytokines, chemokines, endothelial dysfunction and inflammatory mediators are key factors in disease development [4]. Kawasaki disease's inflammatory processes have also been associated with vascular endothelial damage. Increased expression of tumor necrosis factor, interleukins, vascular endothelial growth factors, adhesion molecules and chemokines have been linked to endothelial dysfunction and coronary artery disease in Kawasaki disease [5]. This suggests that a mathematical model that incorporates interactions between endothelial cells, growth factors, chemokines, and cytokines would be relevant. Mathematical models are increasingly used for investigating nonlinear mechanisms of disease. Qiang et al. constructed a differential equation model for Kawasaki disease by considering endothelial cells, vascular endothelial growth factors, adhesion factors, chemokines, and inflammatory factors. Their model exhibited rich dynamics, such as forward and backward bifurcations [6]. Guo et al. also examined the global dynamics of a Kawasaki disease model and confirmed the role of nonlinear feedbacks in sustaining the disease [7]. Delay differential equations are important for modeling non-instantaneous biological processes. In Kawasaki disease, activation of the immune system, release of cytokines, stimulation of the endothelium, and inflammatory feedback processes take time to process. The theory of delay differential equations is an appropriate mathematical formalism to describe such processes [8]. Hence, delay terms can be used to increase biological realism of Kawasaki disease models, by accounting for the time lag between inflammatory stimulation and pathological manifestation. Stochastic analysis is also important due to random variability. Immune system variability, exposure to environmental factors, disease variation and measurement uncertainty can influence disease dynamics. Mao's theory of stochastic differential equations offers standard techniques for establishing positivity, boundedness, extinction and persistence of random dynamical systems [9]. Allen and Gray et al. demonstrated that stochastic epidemic models may lead to extinction or persistence that is not apparent in deterministic models [10,11]. Recent stochastic epidemic research has continued to employ stochastic threshold parameters to determine whether diseases go extinct or persist in the long term [12]. The incidence of Kawasaki disease was altered during the COVID-19 pandemic in various countries. A nationwide survey in Japan showed a marked decrease in Kawasaki disease incidence during the pandemic, followed by a resurgence after the pandemic ended [13–15]. Likewise, Canadian data indicated a decline in 2020–2021 and a return to baseline trends in the subsequent years [16]. This evidence indicates the possibility of the effects of environmental exposure, social contacts and infection control on Kawasaki disease incidence. The pandemic also posed diagnostic challenges because Kawasaki disease has several overlapping inflammatory symptoms with multisystem inflammatory syndrome in children. Comparative studies between pre-pandemic and pandemic periods show variations in clinical and laboratory features and treatment outcomes [17]. These observations give further impetus to use stochastic and delay models because they capture randomness, external disturbances, and time-dependent biological processes. Finite difference methods are needed to solve nonlinear stochastic delay models. Conventional finite difference methods may not always preserve positivity, boundedness and stability. Thus, nonstandard finite difference methods, initially designed to preserve qualitative features of differential equation models, are helpful in biology [18]. In stochastic models, nonstandard schemes maintain non-negativity and stability despite random disturbances, and can be applied to model stochastic Kawasaki disease dynamics. It is important to clarify the biological interpretation of the proposed model. System (1)–(4) is not a population-level epidemiological transmission model. Kawasaki disease is not modeled here as an infectious disease spreading between individuals. Instead, the model

describes within-host, lesion-level interactions among endothelial cells, vascular endothelial growth factors, adhesion molecules/chemokines, and inflammatory cytokines. Therefore, the threshold quantity used in this work should be interpreted as an inflammatory feedback threshold rather than a classical epidemiological inflammatory feedback threshold.

This paper is structured as follows. Section 2 proposes the model with time delay. Section 3 provides a qualitative analysis, including the positivity and boundedness of solutions. Section 4 derives the equilibrium points and the inflammatory feedback threshold. Section 5 deals with the stability analysis of the equilibria. In Section 6, real data from 2020–2025 are analyzed to support the model. Section 7 introduces the stochastic model and its dynamical properties. Section 8 develops the stochastic NSFD scheme. Section 9 illustrates the results through graphical simulations, and Section 10 concludes the study.

2 Model Formulation

The complex interactions between endothelial cells, biochemical mediators, and inflammatory responses play an important role in Kawasaki disease pathogenesis [6]. The deterministic interaction structure used here is based on the Kawasaki disease pathogenesis model proposed by Qiang et al. [6].

In the present study, this baseline framework is extended by introducing a discrete delay in the inflammatory cytokine response, stochastic perturbations, and a structure-preserving numerical approximation. Thus, the biological interaction structure follows the previous Kawasaki disease model, while the delayed stochastic extension and the stochastic NSFD scheme are developed in this work.

It is important to emphasize that the proposed model is not a population-level epidemiological transmission model. Kawasaki disease is not modeled here as a contagious disease spreading between individuals. Instead, the model describes lesion-level inflammatory interaction mechanisms involving endothelial cells, VEGF, adhesion molecules/chemokines, and inflammatory cytokines.

The model does not explicitly divide Kawasaki disease into acute, subacute, and convalescent clinical phases. Coronary artery inflammation is also not included as a separate state variable. Instead, endothelial-cell dysfunction and inflammatory cytokine activity are used as indirect mechanistic indicators of vascular inflammatory progression.

The flow of the state variables and their interactions within the model framework are illustrated in Fig. 1.

Let $E(t)$, $V(t)$, $C(t)$, and $P(t)$ denote the state variables at time t. Their biological meanings are summarized in Table 1.

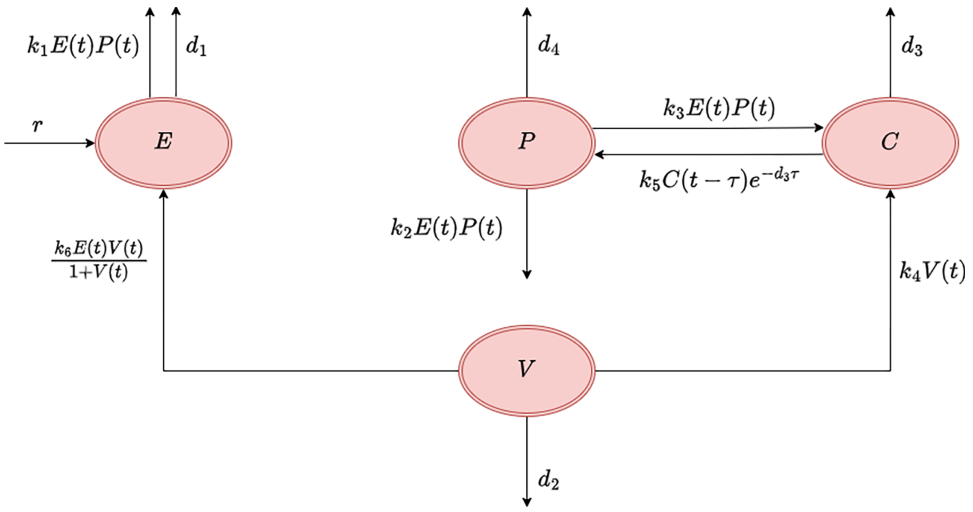

Figure 1: Schematic representation of the proposed lesion-level inflammatory interaction model showing the relationships among endothelial cells, VEGF, adhesion molecules/chemokines, and inflammatory cytokines.

Table 1: State variables of the Kawasaki inflammatory interaction model.

Symbol	Description	Biological Interpretation
$E(t)$	Healthy endothelial-cell activity	Local endothelial-cell condition at time t
$V(t)$	VEGF activity	Vascular endothelial growth factor response
$C(t)$	Adhesion molecule/chemokine activity	Combined inflammatory recruitment signal
$P(t)$	Inflammatory cytokine activity	Aggregated pro-inflammatory cytokine response

The variables represent biological concentrations or activities in the lesion-level inflammatory environment of Kawasaki disease. They do not represent human population classes such as susceptible, infected, or recovered individuals. Therefore, the model describes inflammatory mechanism dynamics rather than epidemiological transmission dynamics. The interaction structure is interpreted as follows. Inflammatory cytokine activity damages healthy endothelial-cell activity through the term $k_1E(t)P(t)$. Endothelial-inflammatory interaction promotes VEGF production through the term $k_2E(t)P(t)$. The same interaction contributes to adhesion molecule/chemokine activation through $k_3E(t)P(t)$, while VEGF further stimulates adhesion molecule/chemokine activity through $k_4V(t)$. Finally, adhesion molecule/chemokine activity drives inflammatory cytokine activation after a delay through the term $k_5C(t-\tau)e^{-d_3\tau}$. The variables are aggregated quantities and do not distinguish individual cytokines such as TNF-α, IL-1, IL-6, or specific adhesion molecules. The delay τ is introduced only in the inflammatory cytokine equation. It represents the time required for adhesion molecule/chemokine activity to produce a measurable inflammatory cytokine response. Biologically, this delay may include intermediate processes such as immune-cell recruitment, intracellular signaling, and cytokine amplification. Other possible delays, such as the delay from endothelial injury to VEGF production or from VEGF activity to adhesion molecule upregulation, are not modeled separately in this formulation. By introducing a discrete delay $\tau > 0$, the deterministic delayed system is given by

$$\frac{dE(t)}{dt} = r + \frac{k_6V(t)E(t)}{1+V(t)} - k_1E(t)P(t) - d_1E(t), \tag{1}$$

$$\frac{dV(t)}{dt} = k_2E(t)P(t) - d_2V(t), \tag{2}$$

$$\frac{dC(t)}{dt} = k_3E(t)P(t) + k_4V(t) - d_3C(t), \tag{3}$$

$$\frac{dP(t)}{dt} = k_5C(t-\tau)e^{-d_3\tau} - d_4P(t). \tag{4}$$

The parameters of system (1)–(4) are summarized in

The numerical values in Table 2 are used only for qualitative simulation experiments. Where direct clinical estimates are unavailable, values are selected from biologically reasonable ranges or adapted from the baseline deterministic model of Qiang et al. [6]. Thus, the simulations should be interpreted as qualitative numerical illustrations rather than patient-specific parameter estimation.

Table 2: Model parameters, biological descriptions, and suggested numerical values used in simulations.

Parameter	Description	Suggested Value	Source/Remark
r	Baseline endothelial-cell regeneration rate	1.5	Simulation value
d_1	Natural decay rate of endothelial-cell activity	4×10^{-1}	Simulation value
d_2	Clearance rate of VEGF activity	6×10^{-1}	Simulation value
d_3	Clearance rate of adhesion molecule/chemokine activity	7×10^{-1}	Simulation value
d_4	Clearance rate of inflammatory cytokine activity	5×10^{-1}	Simulation value
k_1	Cytokine-induced endothelial damage rate	0.8	Adapted/simulation value
k_2	VEGF production rate due to endothelial–inflammatory interaction	1.5	Adapted/simulation value
k_3	Chemokine activation rate due to endothelial–inflammatory interaction	1.2	Adapted/simulation value
k_4	VEGF-induced adhesion molecule/chemokine stimulation rate	0.9	Adapted/simulation value
k_5	Delayed cytokine activation rate from chemokine activity	0.9	Simulation value
k_6	VEGF-mediated endothelial feedback coefficient	0.6	Adapted/simulation value
τ	Delay in inflammatory cytokine response	1.5	Simulation value

In this formulation, r represents the baseline regeneration rate of endothelial-cell activity. The coefficients d_1, d_2, d_3, and d_4 describe the natural decay or clearance rates of the corresponding biological components. The parameter k_1 represents the damaging effect of inflammatory cytokine activity on endothelial-cell activity. The parameters k_2 and k_3 describe the production of VEGF and adhesion molecule/chemokine activity due to endothelial-inflammatory interaction, while k_4 describes the additional

stimulation of adhesion molecule/chemokine activity by VEGF. The parameter k_5 controls delayed inflammatory cytokine activation, and k_6 describes VEGF-mediated endothelial feedback. The delay parameter $\tau > 0$ denotes the average time between adhesion molecule/chemokine activation and the subsequent inflammatory cytokine response. Thus, the delayed term $C(t-\tau)$ represents earlier adhesion molecule/chemokine activity that contributes to cytokine activation at time t. The initial conditions are prescribed on the interval $[-\tau, 0]$ as

$$E(\theta) = \phi_1(\theta), \quad V(\theta) = \phi_2(\theta), \quad C(\theta) = \phi_3(\theta), \quad P(\theta) = \phi_4(\theta), \qquad -\tau \le \theta \le 0, \tag{5}$$

where

$$\phi_i(\theta) \ge 0, \qquad i = 1, 2, 3, 4.$$

3 Qualitative Analysis

In this section, we study the positivity and boundedness of system (1)–(4). Since all state variables represent biological concentrations, the solutions must remain nonnegative and bounded for the model to be biologically meaningful.

$$\mathbb{R}^4_+ = \{(E, V, C, P) \in \mathbb{R}^4 : E \ge 0,\ V \ge 0,\ C \ge 0,\ P \ge 0\}.$$

For the delayed system, we consider the phase space

$$\mathcal{C}_+ = C([-\tau, 0], \mathbb{R}^4_+),$$

with nonnegative initial functions given by (5). In the this manuscript, we do not define the feasible region by the constants M_E, M_V, M_C, and M_P, because such bounds are mutually dependent and therefore circular. Instead, we construct an absorbing positively invariant set using a Lyapunov-type functional.

Theorem 1 (Positivity of solutions): *For any nonnegative initial functions*

$$\phi_i(\theta) \ge 0, \qquad -\tau \le \theta \le 0, \quad i = 1, 2, 3, 4,$$

the solution $(E(t), V(t), C(t), P(t))$ *of system (1)–(4) remains nonnegative for all* $t \ge 0$.

Proof: We verify the vector field on the boundary of the nonnegative orthant. If $E(t) = 0$, then from (1),

$$\left.\frac{dE(t)}{dt}\right|_{E=0} = r > 0.$$

Thus, $E(t)$ cannot become negative. If $V(t) = 0$, then

$$\left.\frac{dV(t)}{dt}\right|_{V=0} = k_2 E(t) P(t) \ge 0.$$

If $C(t) = 0$, then

$$\left.\frac{dC(t)}{dt}\right|_{C=0} = k_3 E(t) P(t) + k_4 V(t) \ge 0.$$

Finally, if $P(t) = 0$, then

$$\left.\frac{dP(t)}{dt}\right|_{P=0} = k_5 C(t-\tau)e^{-d_3\tau} \geq 0.$$

Therefore, the vector field points inward or is tangent on each boundary component of $\mathbb{R}^4_+$. Hence, every solution starting from $\mathcal{C}_+$ remains in $\mathbb{R}^4_+$ for all $t \geq 0$. □

Theorem 2 (Boundedness and positive invariance): *Assume that $d_1 > k_6$. Then every nonnegative solution of system (1)–(4) is ultimately bounded. Moreover, the system admits an absorbing positively invariant set in $\mathcal{C}_+$.*

Proof: Since

$$\frac{V(t)}{1+V(t)} \leq 1,$$

the first equation gives

$$\frac{dE(t)}{dt} \leq r - (d_1 - k_6)E(t).$$

Because $d_1 > k_6$, comparison theory gives

$$\limsup_{t\to\infty} E(t) \leq \frac{r}{d_1 - k_6}.$$

Thus, $E(t)$ is ultimately bounded.

To obtain a non-circular bound for all variables, define

$$\mathcal{W}(t) = E(t) + aV(t) + bC(t) + cP(t) + q\int_{t-\tau}^{t} e^{-\mu(t-s)}C(s)\,ds,$$

where $a, b, c, q, \mu > 0$. Differentiating $\mathcal{W}(t)$ along solutions gives

$$\begin{aligned}\dot{\mathcal{W}}(t) = r &+ \frac{k_6 V(t)E(t)}{1+V(t)} - k_1 E(t)P(t) - d_1 E(t)\\ &+ a\big(k_2 E(t)P(t) - d_2 V(t)\big)\\ &+ b\big(k_3 E(t)P(t) + k_4 V(t) - d_3 C(t)\big)\\ &+ c\big(k_5 e^{-d_3\tau}C(t-\tau) - d_4 P(t)\big)\\ &+ qC(t) - qe^{-\mu\tau}C(t-\tau) - \mu q\int_{t-\tau}^{t} e^{-\mu(t-s)}C(s)\,ds.\end{aligned}$$

Choose

$$q = ck_5 e^{-d_3\tau}e^{\mu\tau}.$$

Then the delayed term $C(t-\tau)$ is cancelled. Using

$$\frac{k_6 V(t)E(t)}{1+V(t)} \leq k_6 E(t),$$

we obtain

$$\begin{aligned}\dot{\mathcal{W}}(t) \leq & r-(d_1-k_6)E(t)-\left(ad_2-bk_4\right)V(t)-\left(bd_3-q\right)C(t)\\ & -cd_4P(t)-\left(k_1-ak_2-bk_3\right)E(t)P(t)\\ & -\mu q\int_{t-\tau}^{t}e^{-\mu(t-s)}C(s)\,ds.\end{aligned}$$

Choose $a, b, c, \mu > 0$ such that

$$ak_2 + bk_3 < k_1, \qquad bk_4 < ad_2, \qquad ck_5e^{-d_3\tau}e^{\mu\tau} < bd_3.$$

Then all negative coefficients above are well-defined and positive. Hence, there exists $\eta > 0$ such that

$$\dot{\mathcal{W}}(t) \leq r - \eta\mathcal{W}(t).$$

By comparison,

$$\mathcal{W}(t) \leq \mathcal{W}(0)e^{-\eta t} + \frac{r}{\eta}\left(1-e^{-\eta t}\right),$$

and therefore

$$\limsup_{t\to\infty}\mathcal{W}(t) \leq \frac{r}{\eta}.$$

Since $\mathcal{W}(t)$ is positive and controls $E(t), V(t), C(t)$, and $P(t)$, all state variables are ultimately bounded.

For any $R \geq r/\eta$, define

$$\Omega_R = \left\{\varphi \in \mathcal{C}_+ : \mathcal{W}(\varphi) \leq R\right\},$$

where

$$\mathcal{W}(\varphi) = \varphi_1(0) + a\varphi_2(0) + b\varphi_3(0) + c\varphi_4(0) + q\int_{-\tau}^{0}e^{\mu\theta}\varphi_3(\theta)\,d\theta.$$

On the boundary $\mathcal{W} = R$,

$$\dot{\mathcal{W}}(t) \leq r - \eta R \leq 0.$$

Therefore, the vector field points inward on the boundary of Ω_R. Thus, Ω_R is positively invariant. Since every solution eventually enters such a set, Ω_R is also absorbing. □

4 Equilibrium Points and Inflammatory Feedback Threshold

Since the delay is constant and equilibrium states are time independent, we have $C(t-\tau) = C^*$ at equilibrium. Therefore, the introduction of the discrete delay does not change the algebraic procedure used to determine the equilibrium points. The equilibrium structure follows the corresponding analysis of Qiang et al. [6]. In the present work, we recall the equilibrium expressions only for completeness and to establish notation for the subsequent delay-dependent stability analysis, stochastic formulation, and numerical approximation. The main modification introduced by the delay appears through the factor $e^{-d_3\tau}$, which

changes the effective threshold quantity. At equilibrium, all time-dependent variables become constant. Hence, the delay term satisfies $C(t-\tau) = C^*$. From (1)–(4), the inflammatory-factor-free equilibrium is

$$\mathcal{E}_0 = (E_0, V_0, C_0, P_0) = \left(\frac{r}{d_1}, 0, 0, 0\right). \tag{6}$$

Following the threshold construction used for the corresponding Kawasaki disease interaction model, we define the inflammatory feedback threshold quantity by considering the coupled variables V, C, and P. This quantity is not a population-level epidemiological reproduction number. Instead, it measures the ability of inflammatory feedback among VEGF, adhesion molecules/chemokines, and inflammatory cytokines to sustain a positive inflammatory state. The effective inflammatory feedback threshold is obtained by applying the next-generation matrix method to the variables V, C, and P. At $\mathcal{E}_0$, we have

$$F = \begin{pmatrix} 0 & 0 & k_2E_0 \\ 0 & 0 & k_3E_0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} d_2 & 0 & 0 \\ -k_4 & d_3 & 0 \\ 0 & -k_5e^{-d_3\tau} & d_4 \end{pmatrix}.$$

Therefore, the inflammatory feedback threshold is

$$\mathcal{R}_0 = \rho(F\mathcal{V}^{-1}) = \frac{rk_5e^{-d_3\tau}(k_2k_4 + d_2k_3)}{d_1d_2d_3d_4}. \tag{7}$$

Thus, a larger value of this threshold indicates stronger inflammatory feedback. The factor $e^{-d_3\tau}$ shows that the delayed chemokine-mediated response modifies the effective inflammatory feedback strength. The factor $e^{-d_3\tau}$ shows that the delay reduces the effective contribution of chemokine-mediated inflammatory activation. Thus, a larger delay τ decreases $\mathcal{R}_0$.

For a positive inflammatory equilibrium

$$\mathcal{E}^* = (E^*, V^*, C^*, P^*),$$

where $V^*, C^*, P^* > 0$, the equilibrium relations give

$$E^* = \frac{d_2d_3d_4e^{d_3\tau}}{k_5(k_2k_4 + d_2k_3)} = \frac{r}{d_1\mathcal{R}_0}. \tag{8}$$

Moreover,

$$P^* = \frac{d_2V^*}{k_2E^*}, \qquad C^* = \frac{d_4e^{d_3\tau}}{k_5}P^*. \tag{9}$$

The value of V^* is obtained from the quadratic equation

$$A(V^*)^2 + BV^* + D = 0, \tag{10}$$

where

$$A = \frac{k_1d_2}{k_2}, \qquad B = \frac{k_1d_2}{k_2} + d_1E^* - r - k_6E^*, \qquad D = d_1E^* - r.$$

Hence,

$$V^* = \frac{-B + \sqrt{B^2 - 4AD}}{2A}, \tag{11}$$

provided that $B^2 - 4AD \geq 0$ and $V^* > 0$. Once V^* is determined, P^* and C^* follow directly from (9). By using (8),

$$E^* = \frac{r}{d_1 \mathcal{R}_0},$$

the coefficients in (10) become

$$A = \frac{k_1 d_2}{k_2},$$
$$B = \frac{k_1 d_2}{k_2} + \frac{r}{\mathcal{R}_0} - r - \frac{k_6 r}{d_1 \mathcal{R}_0},$$

and

$$D = \frac{r}{\mathcal{R}_0} - r = \frac{r(1 - \mathcal{R}_0)}{\mathcal{R}_0}.$$

Therefore,

$$V^* = \frac{-\left(\frac{k_1 d_2}{k_2} + \frac{r}{\mathcal{R}_0} - r - \frac{k_6 r}{d_1 \mathcal{R}_0}\right) + \sqrt{\left(\frac{k_1 d_2}{k_2} + \frac{r}{\mathcal{R}_0} - r - \frac{k_6 r}{d_1 \mathcal{R}_0}\right)^2 - 4\left(\frac{k_1 d_2}{k_2}\right)\left(\frac{r(1-\mathcal{R}_0)}{\mathcal{R}_0}\right)}}{2\left(\frac{k_1 d_2}{k_2}\right)}. \tag{12}$$

Equivalently,

$$V^* = \frac{k_2}{2k_1 d_2}\left[-B + \sqrt{B^2 - \frac{4k_1 d_2 r(1 - \mathcal{R}_0)}{k_2 \mathcal{R}_0}}\right], \tag{13}$$

where

$$B = \frac{k_1 d_2}{k_2} + \frac{r}{\mathcal{R}_0} - r - \frac{k_6 r}{d_1 \mathcal{R}_0}.$$

After obtaining V^*, the remaining components of the inflammatory equilibrium are

$$P^* = \frac{d_2 V^*}{k_2 E^*} = \frac{d_1 d_2 \mathcal{R}_0}{r k_2} V^*, \tag{14}$$

and

$$C^* = \frac{d_4 e^{d_3 \tau}}{k_5} P^* = \frac{d_1 d_2 d_4 \mathcal{R}_0 e^{d_3 \tau}}{r k_2 k_5} V^*. \tag{15}$$

Hence, the inflammatory equilibrium is

$$\mathcal{E}^* = \left(\frac{r}{d_1 \mathcal{R}_0},\ V^*,\ \frac{d_1 d_2 d_4 \mathcal{R}_0 e^{d_3 \tau}}{r k_2 k_5} V^*,\ \frac{d_1 d_2 \mathcal{R}_0}{r k_2} V^*\right). \tag{16}$$

5 Stability Analysis

In this section, we analyze the local and global stability of the inflammatory-factor-free and inflammatory equilibria of the system (1)–(4).

Theorem 3: *The inflammatory-factor-free equilibrium*

$$\mathcal{E}_0 = \left(\frac{r}{d_1}, 0, 0, 0\right)$$

of system (1)–(4) is locally asymptotically stable if $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

Proof: The local stability of $\mathcal{E}_0$ is determined from the linearized delay system. At

$$\mathcal{E}_0 = \left(\frac{r}{d_1}, 0, 0, 0\right),$$

the characteristic equation is

$$(\lambda + d_1)\left[(\lambda + d_2)(\lambda + d_3)(\lambda + d_4) - k_5 E_0 e^{-d_3\tau}\left(k_2 k_4 + k_3(\lambda + d_2)\right) e^{-\lambda\tau}\right] = 0.$$

Thus, one characteristic root is $\lambda = -d_1 < 0$. The remaining roots are given by

$$(\lambda + d_2)(\lambda + d_3)(\lambda + d_4) = k_5 E_0 e^{-d_3\tau}\left(k_2 k_4 + k_3(\lambda + d_2)\right) e^{-\lambda\tau}.$$

Let

$$K = k_5 E_0 e^{-d_3\tau}.$$

Then the above equation becomes

$$(\lambda + d_2)(\lambda + d_3)(\lambda + d_4) = K\left(k_2 k_4 + k_3(\lambda + d_2)\right) e^{-\lambda\tau}.$$

We first prove stability for $\mathcal{R}_0 < 1$. Suppose, to the contrary, that there exists a characteristic root λ with $\mathrm{Re}(\lambda) \geq 0$. Taking moduli on both sides gives

$$|\lambda + d_2|\,|\lambda + d_3|\,|\lambda + d_4| = K\,|k_2 k_4 + k_3(\lambda + d_2)|\,\left|e^{-\lambda\tau}\right|.$$

Since $\mathrm{Re}(\lambda) \geq 0$, we have

$$|e^{-\lambda\tau}| \leq 1, \qquad |\lambda + d_i| \geq d_i, \quad i = 2, 3, 4.$$

Therefore,

$$|\lambda + d_2|\,|\lambda + d_3|\,|\lambda + d_4| \geq |\lambda + d_2| d_3 d_4.$$

On the other hand,

$$K\,|k_2 k_4 + k_3(\lambda + d_2)|\,\left|e^{-\lambda\tau}\right| \leq K\left(k_2 k_4 + k_3|\lambda + d_2|\right).$$

Hence, a root with $\mathrm{Re}(\lambda) \geq 0$ would require

$$|\lambda + d_2| d_3 d_4 \leq K\left(k_2 k_4 + k_3|\lambda + d_2|\right).$$

Let $x = |\lambda + d_2|$. Since $x \geq d_2$, this inequality becomes

$$xd_3d_4 \leq K(k_2k_4 + k_3x).$$

Equivalently,

$$x(d_3d_4 - Kk_3) \leq Kk_2k_4.$$

However, from $\mathcal{R}_0 < 1$, we have

$$\frac{K(k_2k_4 + d_2k_3)}{d_2d_3d_4} < 1,$$

which implies

$$K(k_2k_4 + d_2k_3) < d_2d_3d_4.$$

Hence,

$$d_2(d_3d_4 - Kk_3) > Kk_2k_4.$$

Since $x \geq d_2$, it follows that

$$x(d_3d_4 - Kk_3) \geq d_2(d_3d_4 - Kk_3) > Kk_2k_4.$$

This contradicts the necessary inequality

$$x(d_3d_4 - Kk_3) \leq Kk_2k_4.$$

Therefore, no characteristic root can satisfy $\mathrm{Re}(\lambda) \geq 0$. Hence, all characteristic roots have negative real parts, and $\mathcal{E}_0$ is locally asymptotically stable when $\mathcal{R}_0 < 1$. If $\mathcal{R}_0 > 1$, then

$$K(k_2k_4 + d_2k_3) > d_2d_3d_4.$$

Define

$$G(\lambda) = (\lambda + d_2)(\lambda + d_3)(\lambda + d_4) - K\left(k_2k_4 + k_3(\lambda + d_2)\right)e^{-\lambda\tau}.$$

Then

$$G(0) = d_2d_3d_4 - K(k_2k_4 + d_2k_3) < 0.$$

Moreover,

$$\lim_{\lambda \to +\infty} G(\lambda) = +\infty.$$

By continuity, there exists a positive real root $\lambda > 0$. Therefore, the inflammatory-factor-free equilibrium $\mathcal{E}_0$ is unstable when $\mathcal{R}_0 > 1$. □

Theorem 4: *Let $\mathcal{E}^*$ be a positive inflammatory equilibrium of system (1)–(4). If all characteristic roots of the linearized delay system at $\mathcal{E}^*$ have strictly negative real parts, then $\mathcal{E}^*$ is locally asymptotically stable. If characteristic roots lie on the imaginary axis, the linearized analysis is inconclusive and further center-manifold or bifurcation analysis is required.*

Proof: The local behavior of system (1)–(4) near the positive inflammatory equilibrium $\mathcal{E}^* = (E^*, V^*, C^*, P^*)$ is determined by the Jacobian matrix evaluated at $\mathcal{E}^*$. Since the last equation contains the delayed term $C(t-\tau)$, the linearization introduces the factor $e^{-\lambda\tau}$. Therefore, the delay-Jacobian matrix at $\mathcal{E}^*$ is

$$J(\mathcal{E}^*) = \begin{pmatrix} a_{11} & a_{12} & 0 & a_{14} \\ a_{21} & -d_2 & 0 & a_{24} \\ a_{31} & k_4 & -d_3 & a_{34} \\ 0 & 0 & k_5 e^{-d_3\tau} e^{-\lambda\tau} & -d_4 \end{pmatrix},$$

where

$$a_{11} = \frac{k_6 V^*}{1+V^*} - k_1 P^* - d_1, \qquad a_{12} = \frac{k_6 E^*}{(1+V^*)^2}, \qquad a_{14} = -k_1 E^*,$$
$$a_{21} = k_2 P^*, \qquad a_{24} = k_2 E^*, \qquad a_{31} = k_3 P^*, \qquad a_{34} = k_3 E^*.$$

The eigenvalues are obtained from the characteristic equation

$$\det\left(\lambda I - J(\mathcal{E}^*)\right) = 0.$$

Thus,

$$\begin{vmatrix} \lambda - a_{11} & -a_{12} & 0 & -a_{14} \\ -a_{21} & \lambda + d_2 & 0 & -a_{24} \\ -a_{31} & -k_4 & \lambda + d_3 & -a_{34} \\ 0 & 0 & -k_5 e^{-d_3\tau} e^{-\lambda\tau} & \lambda + d_4 \end{vmatrix} = 0. \tag{17}$$

Expanding (17) along the fourth row gives

$$(\lambda + d_4) \begin{vmatrix} \lambda - a_{11} & -a_{12} & 0 \\ -a_{21} & \lambda + d_2 & 0 \\ -a_{31} & -k_4 & \lambda + d_3 \end{vmatrix} - k_5 e^{-d_3\tau} e^{-\lambda\tau} \begin{vmatrix} \lambda - a_{11} & -a_{12} & -a_{14} \\ -a_{21} & \lambda + d_2 & -a_{24} \\ -a_{31} & -k_4 & -a_{34} \end{vmatrix} = 0. \tag{18}$$

The first determinant in (18) is

$$\begin{vmatrix} \lambda - a_{11} & -a_{12} & 0 \\ -a_{21} & \lambda + d_2 & 0 \\ -a_{31} & -k_4 & \lambda + d_3 \end{vmatrix} = (\lambda + d_3)\left[(\lambda - a_{11})(\lambda + d_2) - a_{12}a_{21}\right].$$

The second determinant is

$$\begin{vmatrix} \lambda - a_{11} & -a_{12} & -a_{14} \\ -a_{21} & \lambda + d_2 & -a_{24} \\ -a_{31} & -k_4 & -a_{34} \end{vmatrix} = a_{14}\left[a_{21}k_4 + a_{31}(\lambda + d_2)\right] + a_{24}\left[k_4(\lambda - a_{11}) + a_{12}a_{31}\right] + a_{34}\left[(\lambda - a_{11})(\lambda + d_2) - a_{12}a_{21}\right].$$

Hence, the characteristic equation can be written as

$$(\lambda + d_4)(\lambda + d_3)\left[(\lambda - a_{11})(\lambda + d_2) - a_{12}a_{21}\right] - k_5 e^{-d_3\tau}e^{-\lambda\tau}Q(\lambda) = 0, \tag{19}$$

where

$$Q(\lambda) = a_{14}\left[a_{21}k_4 + a_{31}(\lambda + d_2)\right] + a_{24}\left[k_4(\lambda - a_{11}) + a_{12}a_{31}\right] + a_{34}\left[(\lambda - a_{11})(\lambda + d_2) - a_{12}a_{21}\right]. \tag{20}$$

Now, expanding the polynomial part, we obtain

$$(\lambda - a_{11})(\lambda + d_2) - a_{12}a_{21} = \lambda^2 + (d_2 - a_{11})\lambda - (a_{11}d_2 + a_{12}a_{21}).$$

Therefore,

$$(\lambda + d_4)(\lambda + d_3) = \lambda^2 + (d_3 + d_4)\lambda + d_3d_4.$$

Thus, the non-delay polynomial part becomes

$$P(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4, \tag{21}$$

where

$$A_1 = d_2 + d_3 + d_4 - a_{11},$$
$$A_2 = d_3d_4 + (d_3 + d_4)(d_2 - a_{11}) - (a_{11}d_2 + a_{12}a_{21}),$$
$$A_3 = d_3d_4(d_2 - a_{11}) - (d_3 + d_4)(a_{11}d_2 + a_{12}a_{21}),$$

and

$$A_4 = -d_3d_4(a_{11}d_2 + a_{12}a_{21}).$$

We emphasize that the above spectral condition is used only as a sufficient mathematical condition for local asymptotic stability of the linearized delayed system. It is not used as a direct biological criterion. Biologically, local stability means that small perturbations in endothelial-cell activity, VEGF, adhesion molecules/chemokines, and inflammatory cytokines decay back toward the steady inflammatory state. Similarly, the delay-dependent polynomial $Q(\lambda)$ can be written as

$$Q(\lambda) = B_2\lambda^2 + B_1\lambda + B_0, \tag{22}$$

where

$$B_2 = a_{34},$$
$$B_1 = a_{14}a_{31} + a_{24}k_4 + a_{34}(d_2 - a_{11}),$$

and

$$B_0 = a_{14}(a_{21}k_4 + a_{31}d_2) + a_{24}(-k_4a_{11} + a_{12}a_{31}) - a_{34}(a_{11}d_2 + a_{12}a_{21}).$$

Consequently, the characteristic equation takes the polynomial-delay form

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 - k_5e^{-d_3\tau}e^{-\lambda\tau}\left(B_2\lambda^2 + B_1\lambda + B_0\right) = 0. \tag{23}$$

The local stability of $\mathcal{E}^*$ is determined by the roots of (23). If all roots λ satisfy

$$\mathrm{Re}(\lambda) < 0,$$

then every sufficiently small perturbation around $\mathcal{E}^*$ decays to zero as $t \to \infty$. Hence, the positive inflammatory equilibrium is locally asymptotically stable.

Furthermore, for $\lambda = i\omega$, we have

$$|e^{-i\omega\tau}| = 1.$$

Hence,

$$\left|k_5e^{-d_3\tau}e^{-i\omega\tau}\left(B_2(i\omega)^2 + B_1(i\omega) + B_0\right)\right| = k_5e^{-d_3\tau}\left|B_2(i\omega)^2 + B_1(i\omega) + B_0\right|.$$

Therefore, a sufficient stability condition is

$$k_5e^{-d_3\tau}\left|B_2(i\omega)^2 + B_1(i\omega) + B_0\right| < \left|(i\omega)^4 + A_1(i\omega)^3 + A_2(i\omega)^2 + A_3(i\omega) + A_4\right|, \quad \forall\omega \geq 0.$$

Under this condition, the delayed feedback term is dominated by the stable polynomial part. Thus, no characteristic root enters the right half-plane, and $\mathcal{E}^*$ remains locally asymptotically stable. Conversely, if at least one characteristic root has positive real part, then some perturbations grow near $\mathcal{E}^*$, and the positive inflammatory equilibrium is unstable. □

Theorem 5: *The inflammatory-factor-free equilibrium*

$$\mathcal{E}_0 = \left(\frac{r}{d_1}, 0, 0, 0\right)$$

of system (1)–(4) is locally asymptotically stable if $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$, *provided that no characteristic root lies on the imaginary axis.*

Proof: The local stability of $\mathcal{E}_0$ is determined from the linearized delay system. At

$$\mathcal{E}_0 = \left(\frac{r}{d_1}, 0, 0, 0\right),$$

the characteristic equation is

$$(\lambda + d_1)\left[(\lambda + d_2)(\lambda + d_3)(\lambda + d_4) - k_5\mathcal{E}_0e^{-d_3\tau}\left(k_2k_4 + k_3(\lambda + d_2)\right)e^{-\lambda\tau}\right] = 0.$$

Hence, one characteristic root is $\lambda = -d_1 < 0$. The remaining characteristic roots satisfy

$$(\lambda + d_2)(\lambda + d_3)(\lambda + d_4) - k_5\mathcal{E}_0 0 e^{-d_3\tau}\left(k_2k_4 + k_3(\lambda + d_2)\right)e^{-\lambda\tau} = 0.$$

At $\lambda = 0$, the left-hand side becomes

$$d_2d_3d_4 - k_5\mathcal{E}_0 e^{-d_3\tau}(k_2k_4 + d_2k_3).$$

Using $\mathcal{E}_0 = r/d_1$, we obtain

$$d_2d_3d_4 - k_5\mathcal{E}_0 e^{-d_3\tau}(k_2k_4 + d_2k_3) = d_2d_3d_4(1 - \mathcal{R}_0).$$

Therefore, $\mathcal{R}_0$ acts as a local threshold quantity near $\mathcal{E}_0$. If $\mathcal{R}_0 > 1$, the characteristic equation admits a positive real root, and hence $\mathcal{E}_0$ is unstable. If $\mathcal{R}_0 < 1$, and all characteristic roots of the linearized delayed system have negative real parts, then $\mathcal{E}_0$ is locally asymptotically stable by the local stability theory of delay differential equations. Because the underlying Kawasaki disease interaction model may exhibit backward bifurcation, the condition $\mathcal{R}_0 < 1$ is not sufficient by itself to guarantee global asymptotic stability. Thus, in the revised manuscript, we do not claim global convergence to $\mathcal{E}_0$ based only on $\mathcal{R}_0 < 1$. □

Remark 1: *The above result is a local stability result. In the present model, $\mathcal{R}_0 < 1$ should not be interpreted as a sufficient condition for global elimination of inflammatory activity. Since backward bifurcation may occur, a positive inflammatory equilibrium can coexist with the inflammatory-factor-free equilibrium for some parameter values. Therefore, additional restrictions are required before any global stability conclusion can be made.*

Theorem 6: *Let*

$$\mathcal{E}^* = (E^*, V^*, C^*, P^*)$$

be a positive inflammatory equilibrium of system (1)–(4). If all characteristic roots of the linearized delay system at $\mathcal{E}^*$ have strictly negative real parts, then $\mathcal{E}^*$ is locally asymptotically stable.

Proof: Let

$$u_1(t) = E(t) - E^*, \quad u_2(t) = V(t) - V^*, \quad u_3(t) = C(t) - C^*, \quad u_4(t) = P(t) - P^*$$

be small perturbations around the positive inflammatory equilibrium $\mathcal{E}^*$. The local behavior of system (1)–(4) near $\mathcal{E}^*$ is determined by the linearized delayed system. Since the fourth equation contains the delayed term $C(t - \tau)$, the linearization introduces the exponential factor $e^{-\lambda\tau}$ in the characteristic equation. The corresponding characteristic equation can be written as

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 - k_5 e^{-d_3\tau}e^{-\lambda\tau}\left(B_2\lambda^2 + B_1\lambda + B_0\right) = 0,$$

where the coefficients A_i and B_i are obtained from the Jacobian matrix evaluated at $\mathcal{E}^*$.

If every characteristic root λ of this equation satisfies

$$\mathrm{Re}(\lambda) < 0,$$

then the zero solution of the linearized perturbation system is asymptotically stable. Therefore, by the local stability theory of delay differential equations, the positive inflammatory equilibrium $\mathcal{E}^*$ is locally asymptotically stable. We emphasize that this result is local. It does not imply global asymptotic stability

in the whole feasible region Ω. A global Lyapunov result would require additional parameter restrictions ensuring that all nonlinear cross-interaction terms are controlled. Since such restrictions are not derived here, no global stability claim is made for $\mathcal{E}^*$. □

6 Reported Incidence Data as Qualitative Motivation

In this section, we summarize recently reported incidence data for Kawasaki disease during and after the COVID-19 pandemic. These data are used only as qualitative motivation for considering variability and delayed biological responses in Kawasaki disease. They are not used to calibrate, estimate, or statistically validate the proposed stochastic delayed model. In particular, the incidence data are population-level observations, whereas system (1)–(4) describes lesion-level inflammatory interactions among endothelial cells, VEGF, adhesion molecules/chemokines, and inflammatory cytokines.

The summary focuses on reported incidence rates among children aged 0 to 4 years, because this age group has the highest reported burden of Kawasaki disease. Published studies indicate that Kawasaki disease incidence decreased during the early COVID-19 pandemic period and subsequently increased after the relaxation of public health measures. In Canada, the pre-pandemic incidence was approximately 22.5 cases per 100,000 children aged 0–4 years, while it declined to 15.8 cases per 100,000 during 2020–2021. The incidence later returned toward the pre-pandemic pattern, reaching approximately 24.1 cases per 100,000 during 2023–2024 [16] (See Table 3). Similarly, data from the national Japanese survey showed a decrease during the pandemic, followed by a marked resurgence after the relaxation of public health measures [13,15].

Table 3: Reported Kawasaki disease incidence trends from recent studies.

Region	Period	Incidence Rate	Main Observation
Canada	Pre-pandemic	22.5 per 100,000	Baseline pattern
Canada	2020–2021	15.8 per 100,000	Pandemic-period reduction
Canada	2023–2024	24.1 per 100,000	Return toward baseline pattern
Japan	2021	269.3 per 100,000	Post-2020 increase
Japan	2022	271.9 per 100,000	Persistently reduced level
Japan	2023	426.7 per 100,000	Strong reported resurgence

The percentage change in incidence was calculated using

$$\%\Delta = \frac{I_2 - I_1}{I_1} \times 100,$$

where I_1 and I_2 denote the baseline and comparison incidence rates, respectively. For Canada, the incidence decreased from 22.5 to 15.8 per 100,000, corresponding to

$$\frac{15.8 - 22.5}{22.5} \times 100 = -29.78\%.$$

This represents an approximately 30% reduction during the early pandemic period. In contrast, the incidence increased from 15.8 in 2020–2021 to 24.1 in 2023–2024, giving

$$\frac{24.1 - 15.8}{15.8} \times 100 = 52.53\%.$$

Thus, the reported post-pandemic period showed a rebound in Kawasaki disease incidence.

For Japan, the reported incidence increased from 269.3 in 2021 to 426.7 per 100,000 children aged 0–4 years in 2023. The relative increase is

$$\frac{426.7 - 269.3}{269.3} \times 100 = 58.45\%.$$

This increase is consistent with reports of a resurgence after the relaxation of pandemic-related restrictions. However, these population-level incidence patterns should not be interpreted as direct validation of the lesion-level mathematical model.

Figs. 2 and 3 show regional and temporal differences in reported Kawasaki disease incidence. The decline during 2020–2021 may be associated with reduced exposure to infectious or environmental triggers during the COVID-19 pandemic, while the later increase may reflect changes following the relaxation of public health restrictions. Japan shows a stronger reported increase than Canada, suggesting region-specific incidence patterns.

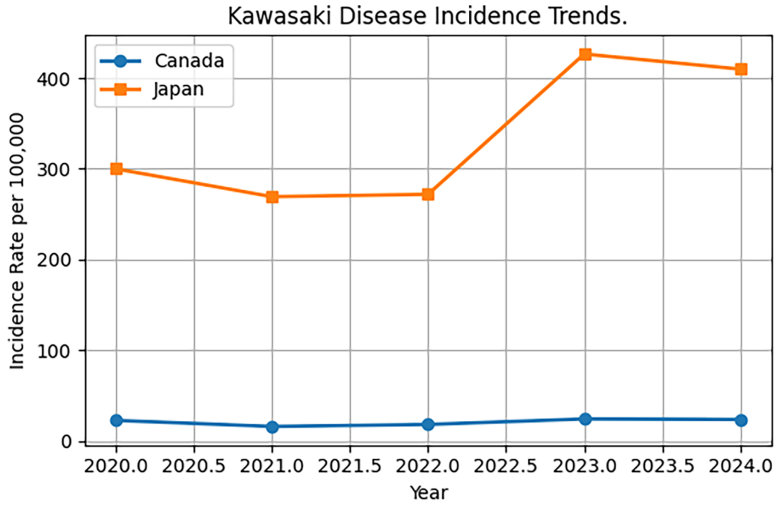

Figure 2: Reported temporal trends of Kawasaki disease incidence in Canada and Japan. The figure provides qualitative motivation only and is not used for model validation.

These figures should be interpreted only as qualitative background motivation. They do not verify the theoretical stability results, do not support a stochastic threshold, and do not validate the stochastic NSFD scheme. The purpose of including these data is to show that Kawasaki disease incidence can vary substantially across time and region, which motivates the mathematical consideration of variability and delayed biological response mechanisms.

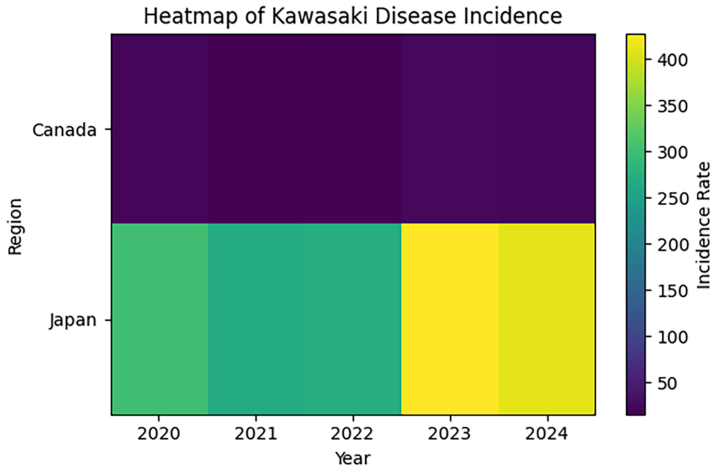

Figure 3: Heatmap representation of reported Kawasaki disease incidence intensity across regions and years. The figure illustrates regional and temporal variation only.

7 Stochastic Model

The stochastic perturbations are introduced to represent random variability in the biological activity of each model component. They are not intended to model a specific infectious agent or environmental exposure as a separate dynamical variable. Instead, the multiplicative noise terms describe unresolved fluctuations in endothelial response, VEGF activity, adhesion molecule/chemokine activation, and inflammatory cytokine activity. Such fluctuations may reflect patient-specific immune variability, local microenvironmental differences, measurement uncertainty, and unmodeled triggering events such as infectious or environmental exposures. To incorporate random fluctuations arising from biological variability, environmental uncertainty, and measurement noise, we extend the deterministic delay system (1)–(4) into a stochastic delay differential equation model. Let $\sigma_1, \sigma_2, \sigma_3, \sigma_4 \geq 0$ denote the noise intensities associated with $E(t)$, $V(t)$, $C(t)$, and $P(t)$, respectively. Let $B_i(t)$, $i = 1, 2, 3, 4$, be mutually independent standard Brownian motions. The stochastic delay model is given by

$$dE(t) = \left[r + \frac{k_6 V(t) E(t)}{1 + V(t)} - k_1 E(t) P(t) - d_1 E(t) \right] dt + \sigma_1 E(t)\, dB_1(t), \tag{24}$$

$$dV(t) = \left[k_2 E(t) P(t) - d_2 V(t) \right] dt + \sigma_2 V(t)\, dB_2(t), \tag{25}$$

$$dC(t) = \left[k_3 E(t) P(t) + k_4 V(t) - d_3 C(t) \right] dt + \sigma_3 C(t)\, dB_3(t), \tag{26}$$

$$dP(t) = \left[k_5 C(t - \tau) e^{-d_3 \tau} - d_4 P(t) \right] dt + \sigma_4 P(t)\, dB_4(t). \tag{27}$$

Here, the stochastic perturbation terms are chosen in proportional form. Thus, the magnitude of the random fluctuation depends on the current level of the corresponding biological variable. In particular, $\sigma_1 E(t) dB_1(t)$ represents random variability in endothelial-cell activity and local injury/repair responses; $\sigma_2 V(t) dB_2(t)$ represents fluctuations in VEGF activity; $\sigma_3 C(t) dB_3(t)$ represents variability in adhesion molecule/chemokine activation; and $\sigma_4 P(t) dB_4(t)$ represents random fluctuations in inflammatory cytokine activity. The parameters σ_i quantify the intensity of these fluctuations.

7.1 Positivity and Boundedness of the Stochastic Delayed Model

Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a complete probability space equipped with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual conditions. Consider the stochastic delayed model (24)–(27) defined on this space.

Let

$$X(t) = \big(E(t), V(t), C(t), P(t)\big),$$

and define the norm

$$|X(t)| = \sqrt{E^2(t) + V^2(t) + C^2(t) + P^2(t)}.$$

We consider the class $C^{2,1}(\mathbb{R}^4_+ \times (0,\infty); \mathbb{R}_+)$ of all nonnegative functions that are twice continuously differentiable in X and once in t.

The stochastic delay system can be written in compact form as

$$dX(t) = F(X(t), t)\, dt + G(X(t), t)\, dW(t), \tag{28}$$

where $F(X,t)$ and $G(X,t)$ denote the drift and diffusion terms, respectively, and $W(t)$ is a standard Brownian motion vector.

Define the differential operator $\mathcal{L}$ associated with (28) by

$$\mathcal{L}V(X,t) = V_t + \sum_{i=1}^{4} F_i(X,t)\frac{\partial V}{\partial X_i} + \frac{1}{2}\sum_{i,j=1}^{4} (GG^T)_{ij}\frac{\partial^2 V}{\partial X_i \partial X_j}.$$

Theorem 7 (Positivity and global existence of the stochastic delayed model): *Assume that the initial functions satisfy*

$$E(\theta) > 0, \quad V(\theta) > 0, \quad C(\theta) > 0, \quad P(\theta) > 0, \qquad -\tau \leq \theta \leq 0.$$

Suppose that $d_1 > k_6$ and that there exist positive constants a, b, c, μ such that

$$ak_2 + bk_3 < k_1, \qquad bk_4 < ad_2, \qquad ck_5 e^{-d_3\tau} e^{\mu\tau} < bd_3.$$

Then system (24)–(27) admits a unique global positive solution. Moreover,

$$(E(t), V(t), C(t), P(t)) \in \mathbb{R}^4_+ \quad \textit{for all } t \geq 0 \quad \textit{a.s.}$$

Proof: The drift and diffusion coefficients of (24)–(27) are locally Lipschitz on $\mathbb{R}^4_+$. Hence, for any positive initial function, there exists a unique local solution on $[0, \tau_e)$, where τ_e denotes the explosion time. We emphasize that the global linear growth condition is not assumed here, because the drift contains bilinear terms such as $E(t)P(t)$. We first prove positivity. Up to the explosion time, the first equation can be written in the linear form

$$dE(t) = [r + A_1(t)E(t)]\, dt + \sigma_1 E(t) dB_1(t),$$

where

$$A_1(t) = \frac{k_6 V(t)}{1 + V(t)} - k_1 P(t) - d_1.$$

By the variation-of-constants formula,

$$E(t) = \Phi_1(t)\left[E(0) + \int_0^t \Phi_1^{-1}(s) r\, ds\right],$$

where

$$\Phi_1(t) = \exp\left(\int_0^t \left(A_1(s) - \frac{\sigma_1^2}{2}\right) ds + \sigma_1 B_1(t)\right) > 0.$$

Therefore, $E(t) > 0$ for $t < \tau_e$. Similarly, the equation for $V(t)$ is

$$dV(t) = [k_2 E(t)P(t) - d_2 V(t)]\, dt + \sigma_2 V(t) dB_2(t).$$

Thus,

$$V(t) = \Phi_2(t)\left[V(0) + \int_0^t \Phi_2^{-1}(s) k_2 E(s) P(s)\, ds\right] > 0,$$

where

$$\Phi_2(t) = \exp\left(\left(-d_2 - \frac{\sigma_2^2}{2}\right) t + \sigma_2 B_2(t)\right) > 0.$$

The same argument gives

$$C(t) = \Phi_3(t)\left[C(0) + \int_0^t \Phi_3^{-1}(s)\big(k_3 E(s)P(s) + k_4 V(s)\big)\, ds\right] > 0,$$

and

$$P(t) = \Phi_4(t)\left[P(0) + \int_0^t \Phi_4^{-1}(s) k_5 e^{-d_3\tau} C(s-\tau)\, ds\right] > 0,$$

where

$$\Phi_3(t) = \exp\left(\left(-d_3 - \frac{\sigma_3^2}{2}\right) t + \sigma_3 B_3(t)\right) > 0$$

and

$$\Phi_4(t) = \exp\left(\left(-d_4 - \frac{\sigma_4^2}{2}\right) t + \sigma_4 B_4(t)\right) > 0.$$

Since the initial function is positive on $[-\tau, 0]$, it follows that $C(s-\tau) > 0$ whenever the delayed term is used. Hence, all components remain positive up to τ_e. It remains to prove that $\tau_e = \infty$ almost surely. Define the Lyapunov functional

$$\mathcal{W}(t) = E(t) + aV(t) + bC(t) + cP(t) + q\int_{t-\tau}^t e^{-\mu(t-s)} C(s)\, ds,$$

where

$$q = ck_5 e^{-d_3\tau} e^{\mu\tau}.$$

Applying Itô's formula to $\mathcal{W}(t)$, we obtain

$$d\mathcal{W}(t) = \mathcal{A}\mathcal{W}(t)\,dt + \sigma_1 E(t)dB_1(t) + a\sigma_2 V(t)dB_2(t) + b\sigma_3 C(t)dB_3(t) + c\sigma_4 P(t)dB_4(t),$$

where $\mathcal{A}$ denotes the infinitesimal generator applied to the drift part. Since $\mathcal{W}$ is linear in the current state variables, the second-order Itô correction terms vanish. Using

$$\frac{k_6 V(t)E(t)}{1+V(t)} \le k_6 E(t),$$

and the choice of q, the delayed term $C(t-\tau)$ is cancelled. Hence,

$$\begin{aligned}\mathcal{A}\mathcal{W}(t) \le & r - (d_1 - k_6)E(t) - \big(ad_2 - bk_4\big)V(t) - \big(bd_3 - q\big)C(t) \\ & - cd_4 P(t) - \big(k_1 - ak_2 - bk_3\big)E(t)P(t) \\ & - \mu q \int_{t-\tau}^{t} e^{-\mu(t-s)} C(s)\,ds.\end{aligned}$$

By the assumed inequalities,

$$ak_2 + bk_3 < k_1, \qquad bk_4 < ad_2, \qquad q < bd_3,$$

all nonlinear and coupling terms are controlled. Therefore, there exists $\eta > 0$ such that

$$\mathcal{A}\mathcal{W}(t) \le r - \eta\mathcal{W}(t).$$

Thus,

$$d\mathcal{W}(t) \le (r - \eta\mathcal{W}(t))\,dt + dM(t),$$

where

$$dM(t) = \sigma_1 E(t)dB_1(t) + a\sigma_2 V(t)dB_2(t) + b\sigma_3 C(t)dB_3(t) + c\sigma_4 P(t)dB_4(t)$$

is a local martingale term. For $m > 1$, define the stopping time

$$\tau_m = \inf\left\{t \in [0, \tau_e) : E(t) + V(t) + C(t) + P(t) \ge m\right\}.$$

Integrating up to $t \wedge \tau_m$ and taking expectations, the martingale term has zero expectation. Hence,

$$\mathbb{E}\mathcal{W}(t \wedge \tau_m) \le \mathcal{W}(0) + rt.$$

A sharper estimate obtained from the differential inequality gives

$$\mathbb{E}\mathcal{W}(t \wedge \tau_m) \le \mathcal{W}(0)e^{-\eta t} + \frac{r}{\eta}\left(1 - e^{-\eta t}\right) \le \mathcal{W}(0) + \frac{r}{\eta}.$$

Since $\mathcal{W}(t)$ controls $E(t) + V(t) + C(t) + P(t)$ from below, there exists a constant $K_0 > 0$ such that

$$\mathcal{W}(t) \ge K_0\big(E(t) + V(t) + C(t) + P(t)\big).$$

On the event $\{\tau_m \le T\}$, we have

$$\mathcal{W}(\tau_m) \ge K_0 m.$$

Therefore,

$$K_0 m\, \mathbb{P}(\tau_m \le T) \le \mathbb{E}\mathcal{W}(T \wedge \tau_m) \le \mathcal{W}(0) + \frac{r}{\eta}.$$

Letting $m \to \infty$, we obtain

$$\mathbb{P}(\tau_m \le T) \to 0.$$

Since $T > 0$ is arbitrary, it follows that $\tau_e = \infty$ almost surely. Thus, the local positive solution is global and remains positive for all $t \ge 0$. □

7.2 Scope of the Stochastic Stability Analysis

In the previous version, extinction and persistence results were stated for the stochastic delayed model (24)–(27) by introducing a stochastic threshold quantity. However, a rigorous stochastic threshold must be derived from stochastic linearization, a logarithmic Lyapunov functional, or Lyapunov exponent analysis. Since the present model contains nonlinear drift terms, delay terms, and multiplicative noise, such a derivation requires a separate analysis.

Therefore, in the revised manuscript, we do not introduce the stochastic threshold $\mathcal{R}_s$. We also do not claim mean-square exponential stability, almost-sure extinction, or persistence in the mean. These are distinct stochastic stability concepts and each requires its own precise definition and proof. To avoid unsupported claims, the stochastic analysis in this work is restricted to positivity, global existence, and non-explosion of solutions under the Lyapunov-type dissipativity conditions stated in Theorem 7.

For clarity, we use the following terminology. A stochastic process

$$X(t) = (E(t), V(t), C(t), P(t))$$

is called a local solution of (24)–(27) if there exists a stopping time $\tau_e > 0$ such that $X(t)$ satisfies the stochastic delayed system for $0 \le t < \tau_e$ almost surely.

The solution is called positive if, for positive initial functions

$$E(\theta) > 0, \quad V(\theta) > 0, \quad C(\theta) > 0, \quad P(\theta) > 0, \qquad -\tau \le \theta \le 0,$$

one has

$$E(t) > 0, \quad V(t) > 0, \quad C(t) > 0, \quad P(t) > 0, \qquad t \ge 0,$$

almost surely.

The solution is called non-explosive if the explosion time satisfies

$$\tau_e = \infty \quad \text{a.s.}$$

Equivalently, the solution exists globally in time almost surely.

Thus, the stochastic results in the revised manuscript are limited to:

- local existence and uniqueness under local Lipschitz continuity of the drift and diffusion coefficients;
- positivity of solutions for positive initial functions;
- global non-explosion under the Lyapunov-type dissipativity assumptions stated in Theorem 7.

The drift coefficients of the stochastic delayed model contain nonlinear bilinear terms such as $E(t)P(t)$. Hence, a stochastic threshold for extinction or persistence cannot be obtained merely by subtracting a noise correction term from the deterministic threshold. A complete analysis of stochastic extinction and persistence for the delayed Kawasaki inflammatory interaction model would require a separate study based on the top Lyapunov exponent or an appropriate logarithmic Lyapunov functional. This issue is left for future research.

8 Stochastic Nonstandard Finite Difference Scheme

To numerically approximate the stochastic delayed model (24)–(27), we construct a stochastic NSFD-type scheme. The deterministic drift part is discretized using nonstandard finite difference principles, while the stochastic perturbations are included through Brownian increments in the sense of an Euler–Maruyama-type approximation. Thus, the proposed method combines an NSFD treatment of the deterministic drift with a standard discrete approximation of the Itô noise. The term stochastic NSFD-type scheme is used here because the classical NSFD framework is deterministic. Its extension to stochastic differential equations is nontrivial. In the present construction, the NSFD features are the use of a nonstandard denominator function, nonlocal treatment of nonlinear terms, and implicit treatment of decay terms. The stochastic component is incorporated by the increments of Brownian motion. The purpose of the scheme is to improve the preservation of positivity, boundedness, and qualitative consistency in numerical simulations. Let

$$t_n = nh, \qquad E_n \simeq E(t_n), \quad V_n \simeq V(t_n), \quad C_n \simeq C(t_n), \quad P_n \simeq P(t_n).$$

Assume that $\tau = mh$, where $m \in \mathbb{N}$. Then

$$C(t_n - \tau) \simeq C_{n-m}.$$

The Brownian increments are defined by

$$\Delta B_{i,n} = B_i(t_{n+1}) - B_i(t_n) = \sqrt{h}\,\xi_{i,n}, \qquad i = 1, 2, 3, 4,$$

where

$$\xi_{i,n} \sim \mathcal{N}(0,1)$$

are independent standard normal random variables.

Define the NSFD denominator function by

$$\Phi(h) = \frac{1 - e^{-\rho h}}{\rho}, \qquad \rho > 0.$$

Then

$$\Phi(h) = h + \mathcal{O}(h^2), \qquad h \to 0,$$

so the scheme remains consistent with the continuous-time model.

In the following construction, production terms are evaluated at known time levels, while decay and loss terms are treated implicitly at the new time level. This produces positive denominators in the update formulas. The stochastic terms are evaluated at time level n, as in an Euler–Maruyama-type approximation.

The stochastic NSFD-type discretization of the E-equation is

$$\frac{E_{n+1}-E_n}{\Phi(h)} = r + \frac{k_6 V_n E_n}{1+V_n} - k_1 E_{n+1} P_n - d_1 E_{n+1} + \sigma_1 E_n \frac{\Delta B_{1,n}}{\Phi(h)}. \tag{29}$$

Hence,

$$E_{n+1} = \frac{E_n + \Phi(h)\left(r + \dfrac{k_6 V_n E_n}{1+V_n}\right) + \sigma_1 E_n \Delta B_{1,n}}{1+\Phi(h)(k_1 P_n + d_1)}. \tag{30}$$

Similarly, for $V(t)$, we use

$$\frac{V_{n+1}-V_n}{\Phi(h)} = k_2 E_n P_n - d_2 V_{n+1} + \sigma_2 V_n \frac{\Delta B_{2,n}}{\Phi(h)}, \tag{31}$$

which gives

$$V_{n+1} = \frac{V_n + \Phi(h) k_2 E_n P_n + \sigma_2 V_n \Delta B_{2,n}}{1+\Phi(h) d_2}. \tag{32}$$

For $C(t)$, the scheme is

$$\frac{C_{n+1}-C_n}{\Phi(h)} = k_3 E_n P_n + k_4 V_n - d_3 C_{n+1} + \sigma_3 C_n \frac{\Delta B_{3,n}}{\Phi(h)}, \tag{33}$$

and therefore

$$C_{n+1} = \frac{C_n + \Phi(h)(k_3 E_n P_n + k_4 V_n) + \sigma_3 C_n \Delta B_{3,n}}{1+\Phi(h) d_3}. \tag{34}$$

For the delayed inflammatory cytokine component, we write

$$\frac{P_{n+1}-P_n}{\Phi(h)} = k_5 C_{n-m} e^{-d_3 \tau} - d_4 P_{n+1} + \sigma_4 P_n \frac{\Delta B_{4,n}}{\Phi(h)}. \tag{35}$$

Thus,

$$P_{n+1} = \frac{P_n + \Phi(h) k_5 C_{n-m} e^{-d_3 \tau} + \sigma_4 P_n \Delta B_{4,n}}{1+\Phi(h) d_4}. \tag{36}$$

The discrete initial functions are prescribed by

$$E_j = \phi_1(t_j), \qquad V_j = \phi_2(t_j), \qquad C_j = \phi_3(t_j), \qquad P_j = \phi_4(t_j), \qquad j = -m, -m+1, \ldots, 0.$$

Eqs. (30)–(36) define the stochastic NSFD-type approximation of the delayed stochastic model.

The update formulas show that the deterministic loss terms are treated implicitly through the positive denominators

$$1+\Phi(h)(k_1P_n+d_1),\qquad 1+\Phi(h)d_2,\qquad 1+\Phi(h)d_3,\qquad 1+\Phi(h)d_4.$$

This is the main NSFD feature of the scheme. The random perturbations are included through the multiplicative terms $\sigma_i X_{i,n}\Delta B_{i,n}$. Because Gaussian Brownian increments are unbounded, unconditional pathwise positivity cannot be claimed for arbitrary step size and arbitrary noise intensity. Positivity must therefore be understood under suitable stepwise admissibility conditions or through a truncated-increment implementation.

8.1 Qualitative Properties of the Stochastic NSFD-Type Scheme

In this subsection, we state the qualitative properties of the proposed stochastic NSFD-type scheme. Since the stochastic increments are Gaussian and unbounded, the deterministic positivity argument used for classical NSFD schemes does not automatically apply. We therefore state positivity under explicit admissibility conditions on the stochastic increments.

Theorem 8 (Conditional positivity): *Assume that the discrete initial data are nonnegative. Suppose that, for each time step n, the stochastic increments satisfy the admissibility conditions*

$$E_n+\Phi(h)\left(r+\frac{k_6V_nE_n}{1+V_n}\right)+\sigma_1E_n\Delta B_{1,n}\geq 0,$$
$$V_n+\Phi(h)k_2E_nP_n+\sigma_2V_n\Delta B_{2,n}\geq 0,$$
$$C_n+\Phi(h)(k_3E_nP_n+k_4V_n)+\sigma_3C_n\Delta B_{3,n}\geq 0,$$

and

$$P_n+\Phi(h)k_5C_{n-m}e^{-d_3\tau}+\sigma_4P_n\Delta B_{4,n}\geq 0.$$

Then the numerical solution generated by (30)–(36) remains nonnegative, that is,

$$E_{n+1}\geq 0,\qquad V_{n+1}\geq 0,\qquad C_{n+1}\geq 0,\qquad P_{n+1}\geq 0.$$

Proof: The denominators in (30)–(36) are

$$1+\Phi(h)(k_1P_n+d_1),\qquad 1+\Phi(h)d_2,\qquad 1+\Phi(h)d_3,\qquad 1+\Phi(h)d_4.$$

These denominators are strictly positive for $h>0$, $\rho>0$, and nonnegative P_n. Under the stated admissibility conditions, all numerators are nonnegative. Hence, each updated component is nonnegative. By induction, the discrete solution remains nonnegative as long as the admissibility conditions hold at each step. □

For practical simulations, the admissibility conditions can be promoted by using sufficiently small time steps and moderate noise intensities. Alternatively, one may use truncated Brownian increments

$$\Delta B_{i,n}^{T}=\max\{-\ell_i,\min(\Delta B_{i,n},\ell_i)\},$$

where the truncation levels $\ell_i>0$ are chosen so that the corresponding numerators remain nonnegative. This truncated version gives a positivity- oriented implementation of the stochastic NSFD-type scheme.

Theorem 9 (Mean boundedness under admissible increments): *Assume that the numerical solution remains nonnegative and that the stochastic increments are either admissible or truncated so that the update formulas remain well defined. If the coefficients satisfy a discrete dissipativity condition analogous to the continuous Lyapunov condition, then the stochastic NSFD-type scheme is bounded in mean on every finite time interval.*

Proof: Define the discrete Lyapunov quantity

$$\mathcal{W}_n = E_n + aV_n + bC_n + cP_n + q \sum_{j=n-m}^{n} e^{-\mu(t_n - t_j)} C_j h,$$

where $a, b, c, q, \mu > 0$ are chosen as in the continuous dissipativity argument. Using the update Formulas (30)–(36), the implicit decay terms and the delayed contribution can be arranged so that

$$\mathbb{E}[\mathcal{W}_{n+1} \mid \mathcal{F}_{t_n}] \le (1 - \eta\Phi(h))\mathcal{W}_n + \Phi(h)r,$$

for some $\eta > 0$, provided h is chosen so that $1 - \eta\Phi(h) \ge 0$. Taking expectations gives

$$\mathbb{E}[\mathcal{W}_{n+1}] \le (1 - \eta\Phi(h))\mathbb{E}[\mathcal{W}_n] + \Phi(h)r.$$

Iterating this inequality yields

$$\mathbb{E}[\mathcal{W}_n] \le (1 - \eta\Phi(h))^n \mathbb{E}[\mathcal{W}_0] + \frac{r}{\eta}\left[1 - (1 - \eta\Phi(h))^n\right].$$

Therefore, $\mathbb{E}[\mathcal{W}_n]$ remains bounded on finite time intervals, and the numerical solution is bounded in mean under the stated admissibility and dissipativity assumptions. □

The above boundedness result is a qualitative numerical estimate. It should not be interpreted as an unconditional almost-sure stability theorem for the stochastic scheme. Because Brownian increments are unbounded, unconditional pathwise positivity and global boundedness require additional assumptions, such as truncated increments or suitable taming of the stochastic terms.

9 Graphical Simulation

The numerical simulations in this section are intended to illustrate the qualitative behavior of the proposed delayed stochastic inflammatory interaction model under selected parameter values. They are not intended to predict population-level Kawasaki disease incidence. Instead, the simulations examine how endothelial cells, VEGF, adhesion molecules/chemokines, and inflammatory cytokines respond to time delay, stochastic perturbations, and different numerical discretization methods. The comparison among Euler–Maruyama, stochastic Runge–Kutta, and stochastic NSFD schemes is included to assess whether the numerical methods preserve positivity, boundedness, and stable long-time behavior of the biological variables. The graphical analysis provides a clear visualization of the dynamic behavior of the proposed model under different numerical approaches and parameter settings. The simulation results highlight the evolution of all state variables over time and demonstrate how the system responds to stochastic perturbations and delay effects.

9.1 Discussion

In the figures, $E(t)$ denotes healthy endothelial-cell activity, $V(t)$ denotes VEGF concentration, $C(t)$ denotes the combined activity of adhesion molecules and chemokines, and $P(t)$ denotes inflammatory cytokine activity. Therefore, boundedness and positivity of these variables are necessary for biological

consistency of the simulated inflammatory process. The simulations are designed to clarify the qualitative behavior of the lesion-level inflammatory interaction model and the performance of the proposed stochastic NSFD scheme. They should not be interpreted as population-level epidemiological predictions for Kawasaki disease incidence. Fig. 4 shows the time evolution of all state variables $E(t)$, $V(t)$, $C(t)$, and $P(t)$ under stochastic perturbations. The variables settle into bounded fluctuating regions after some transient, thus showing the long-term boundedness of the stochastic solution. The same dynamics are illustrated in a heatmap fashion in Fig. 5, with the relative magnitudes of the four state variables being emphasized with respect to the time evolution. Fig. 6 shows the three-dimensional phase trajectory in the (E, V, P)-space. The trajectory tends to move towards a bounded region in the phase plane, indicating that the long-term dynamics are stable. Fig. 7 illustrates the numerical error for different step sizes. The error observed is non-monotonic, so more effort is needed in the calculation of the error and in comparing it with a sufficiently accurate reference solution to come to a definite conclusion regarding the convergence order. Fig. 8 presents a comparison of the Euler-Maruyama, stochastic Runge-Kutta, stochastic NSFD and deterministic solutions for the inflammatory component $P(t)$ at $\tau = 1.5$ and $h = 0.10$. All the numerical solutions oscillate about the equilibrium solution and the NSFD solution is positive and is bounded. The NSFD trajectories of all of the state variables are shown in Fig. 9 along with the equilibrium values. The solutions approach bounded neighbourhoods of the equilibria as expected from a stochastic system. The total concentration $E(t) + V(t) + C(t) + P(t)$ is plotted in Fig. 10. The total concentration is initially increased and stayed bounded, which proves the boundedness of the numerical scheme. The effect of the delay parameter τ on $P(t)$ is illustrated in Fig. 11. The long term level of the inflammatory part is considerably decreased with a larger delay, as is consistent with the attenuation factor $e^{-d_3\tau}$ that is present in the model. In this case (stochastic intensity) the influence of this parameter on $P(t)$ is explored via Fig. 12. An increase in the noise intensity leads to more pronounced random fluctuations around the equilibrium region; however, the dynamics of the numbers do not escape from the boundaries of the region. A three-dimensional phase portrait is displayed in Fig. 13 and it reveals that the trajectory moves towards a neighbourhood of the endemic equilibrium. The NSFD dynamics are shown in a heatmap in Fig. 14 to illustrate that all of the state variables are confined within bounds throughout the simulation. Finally, the behavior of the numerical methods towards an equilibrium band is compared in Fig. 15. The figure shows the differences in the temporal stability of the numerical solutions of the problem, but further simulations with other step sizes must still be performed to determine whether this is also stable with respect to the step size. Overall, the simulations demonstrate the qualitative behavior of the model and the numerical reliability of the proposed scheme, rather than making epidemiological incidence predictions.

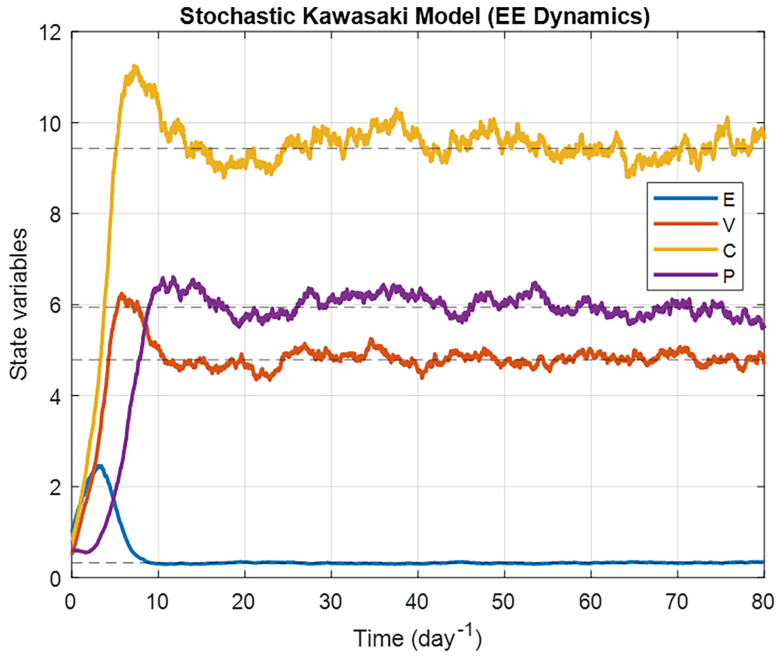

Figure 4: Time evolution of all state variables $E(t)$, $V(t)$, $C(t)$, and $P(t)$ under stochastic perturbations, demonstrating transient dynamics and bounded long-term behavior.

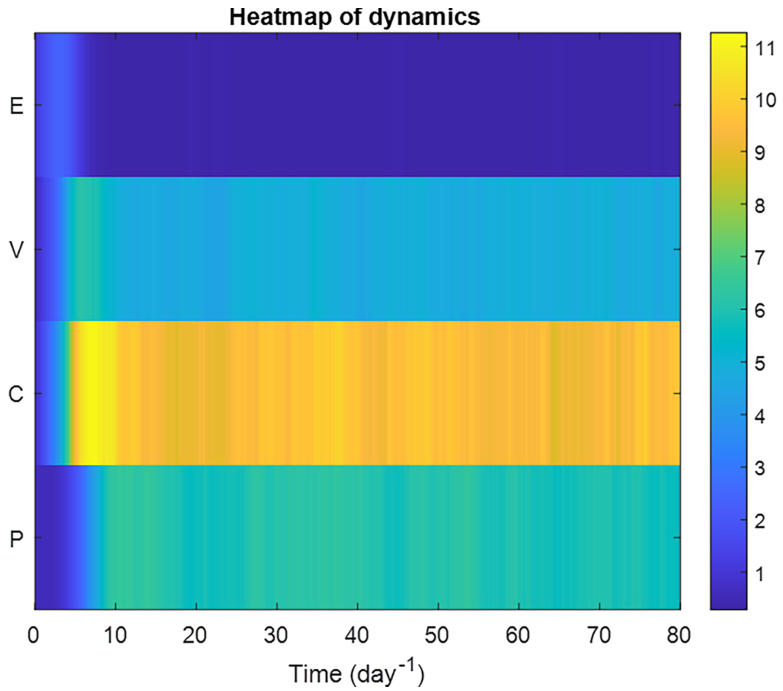

Figure 5: Heatmap of the temporal evolution of $E(t)$, $V(t)$, $C(t)$, and $P(t)$, showing their relative magnitudes and bounded stochastic variations.

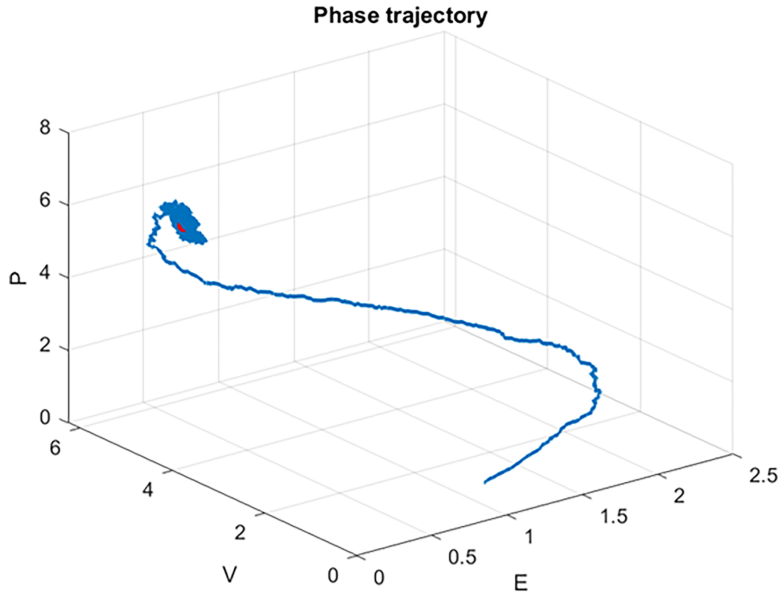

Figure 6: Three-dimensional phase trajectory in the (E, V, P)-space illustrating convergence toward a bounded attractor region.

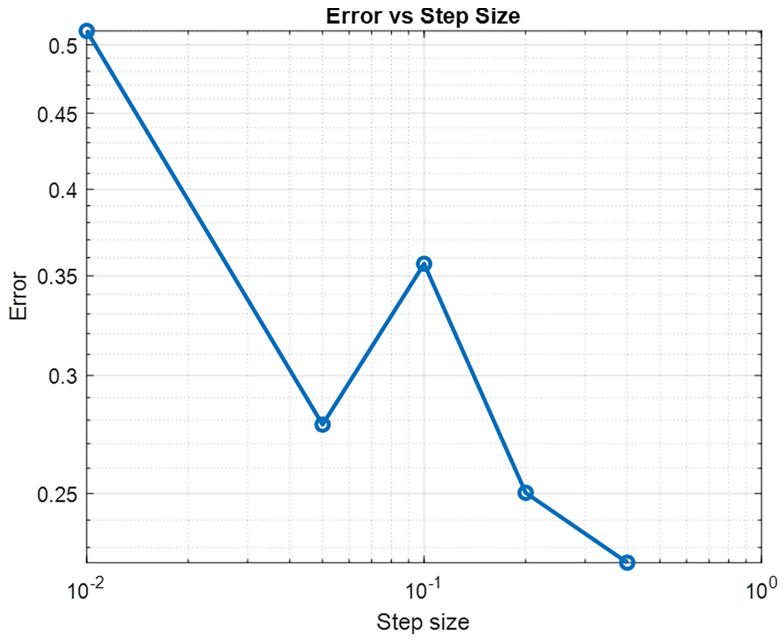

Figure 7: Numerical error as a function of the step size, showing non-monotonic variation in the computed error.

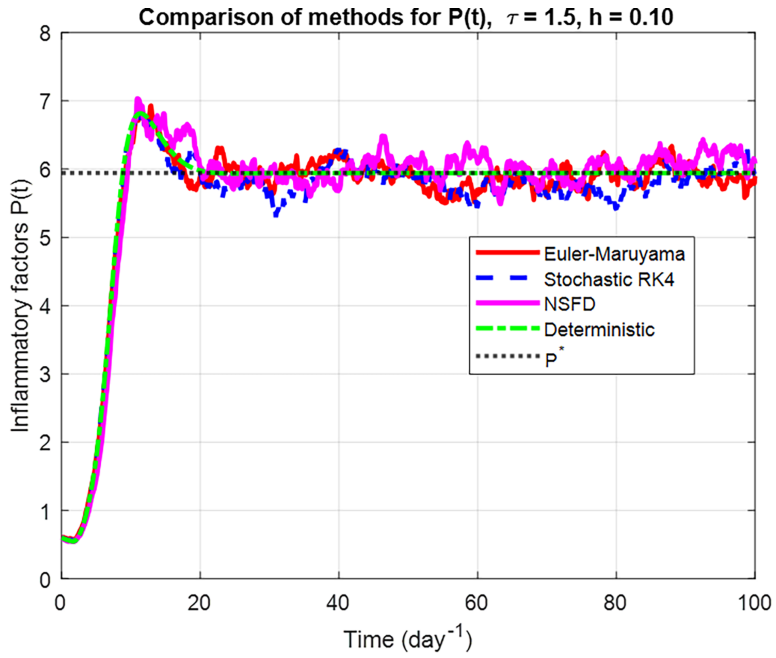

Figure 8: Comparison of Euler–Maruyama, stochastic RK4, NSFD, and deterministic solutions for $P(t)$ at $\tau = 1.5$ and $h = 0.10$.

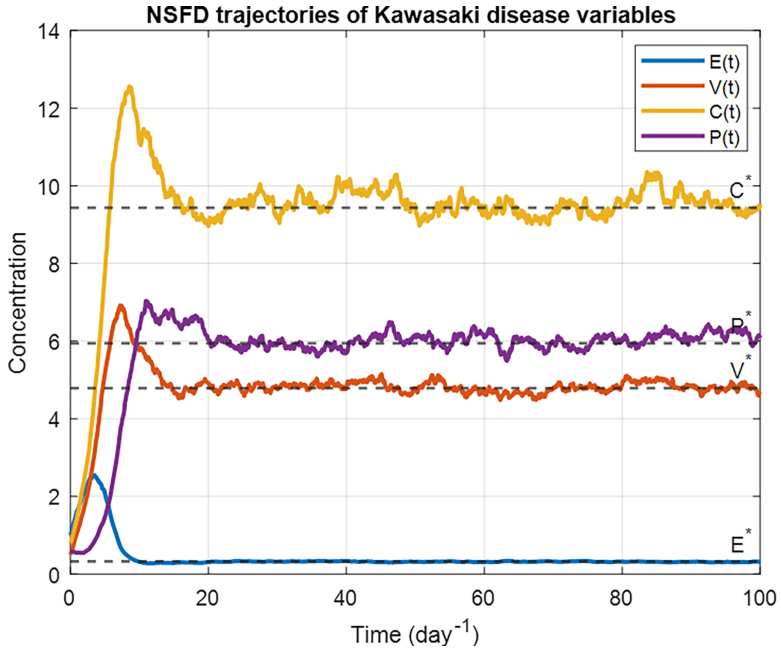

Figure 9: NSFD trajectories of all state variables showing convergence toward bounded neighbourhoods of their corresponding equilibrium values.

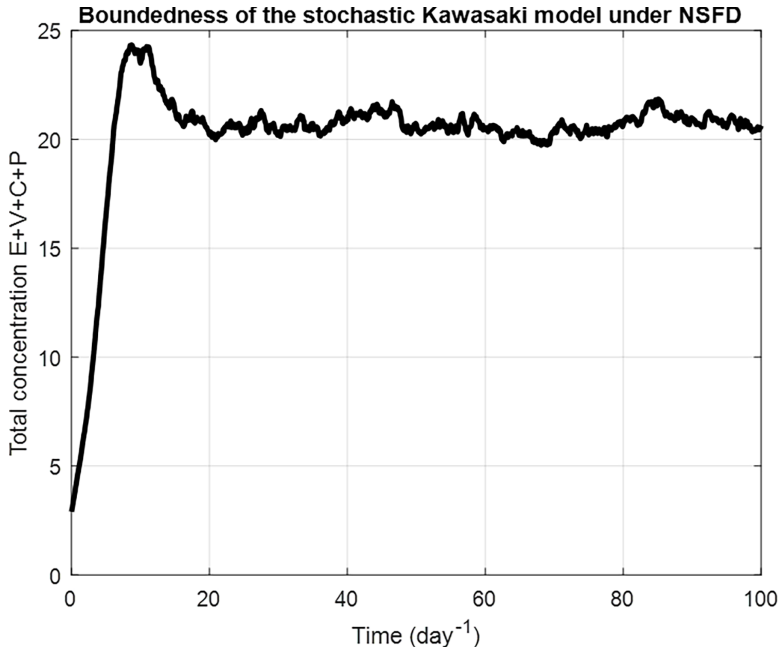

Figure 10: Temporal evolution of the total concentration, confirming the boundedness of the stochastic NSFD solution.

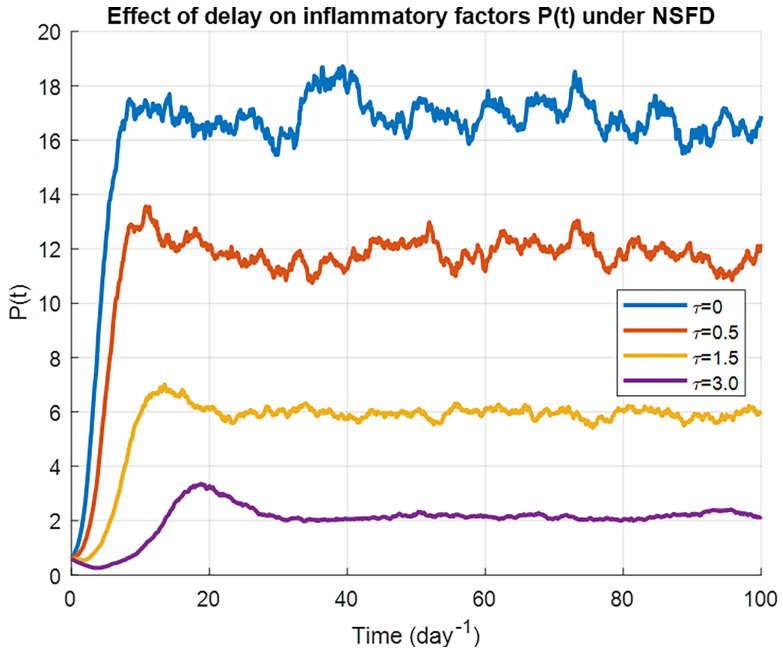

Figure 11: Effect of the time delay τ on the inflammatory component $P(t)$, showing a reduction in its long-term level as the delay increases.

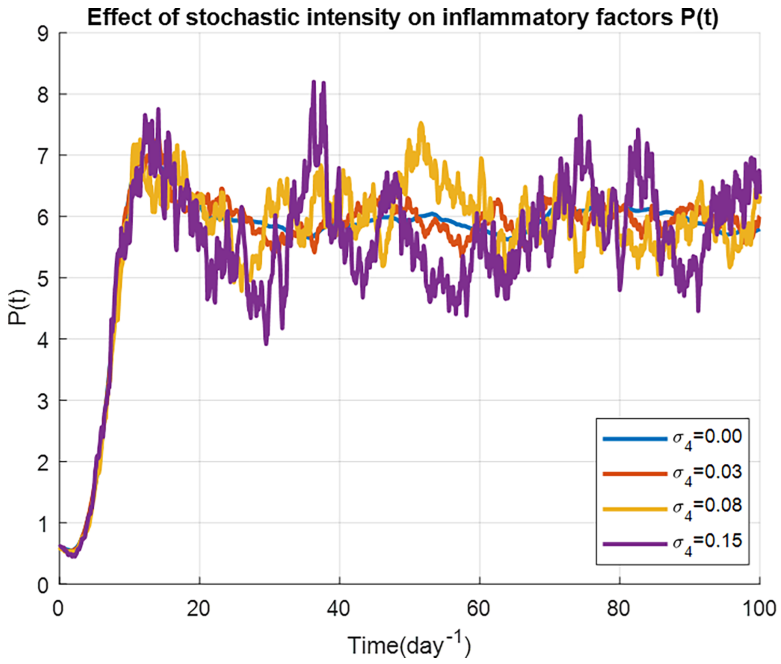

Figure 12: Effect of stochastic intensity σ_4 on $P(t)$, where increasing noise intensity produces greater random variability while the trajectories remain bounded.

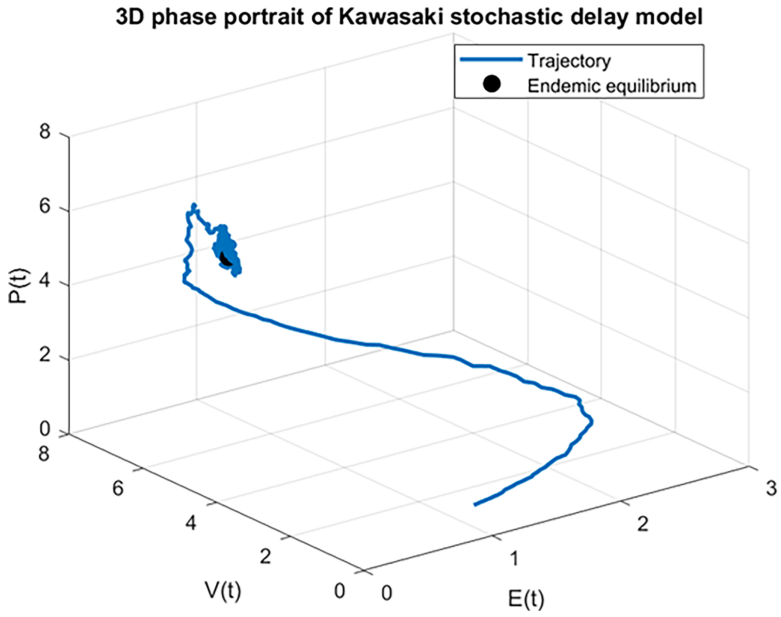

Figure 13: Three-dimensional phase portrait of the stochastic delay model showing convergence toward a neighbourhood of the endemic equilibrium.

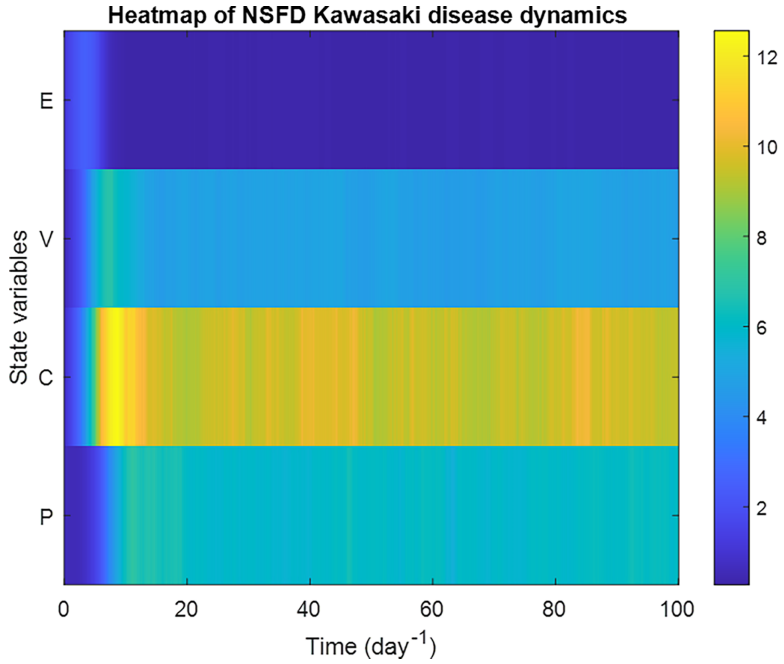

Figure 14: Heatmap of the NSFD solution showing the temporal evolution and bounded variation of all state variables.

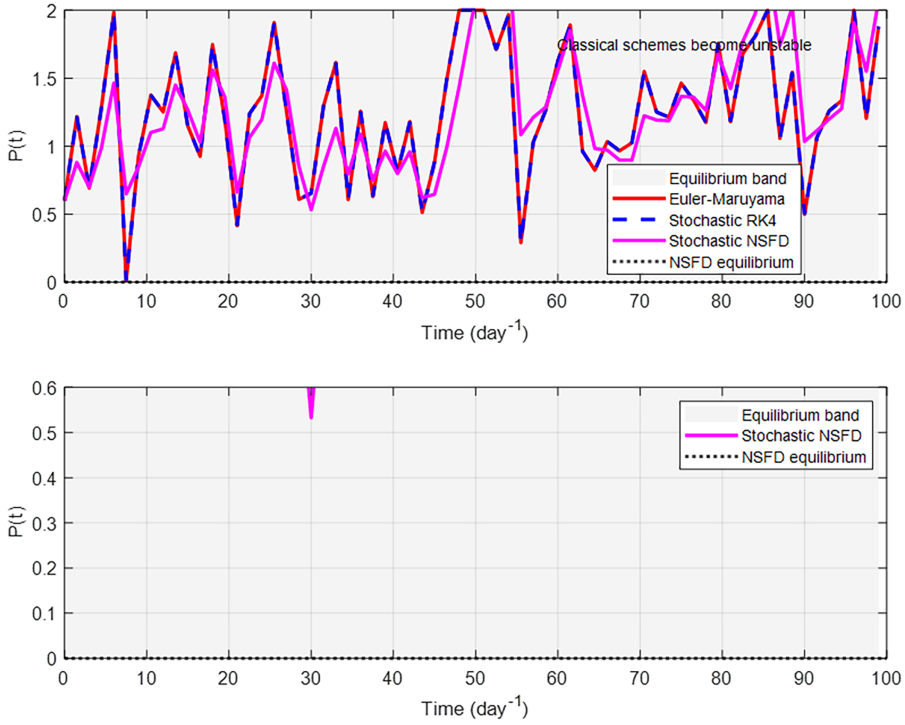

Figure 15: Comparison of numerical trajectories relative to the equilibrium band, illustrating differences in the stability behavior of the classical and NSFD schemes.

10 Conclusion

This study formulated a stochastic delay mathematical model to understand the mechanism of Kawasaki disease in terms of interactions between endothelial cells, vascular endothelial growth factors (VEGF), adhesion molecules (AM), chemokines (CK) and inflammatory cytokines (IC). The model considered time delays and stochastic effects to account for the delay of biological processes and variability of immune-inflammatory responses. Qualitative analysis demonstrated that the solutions are positive and bound in the biologically feasible region. The inflammatory-factor-free and positive inflammatory equilibria were found, and the inflammatory feedback threshold was calculated as a threshold value for disappearance of inflammatory activity or persistence. The stability of the disease-free and endemic equilibria revealed that the disease-free state is stable if the threshold quantity is less than unity, and persistence of inflammatory activity may be observed if the threshold is greater than unity. Analysis of the real data from 2020–2025 confirmed the effects of the randomness and delay, and showed different patterns of Kawasaki disease during and after the pandemic. Additionally, a stochastic NSFD scheme was proposed to preserve the properties of the continuous model (positivity, boundedness and stability). Numerical simulations confirmed the analytical results and showed that the model framework is able to reproduce the mean dynamics and random fluctuations. In conclusion, the model provides a mathematical framework for studying lesion-level inflammatory interactions in Kawasaki disease and may support future theoretical research on endothelial dysfunction, immune-inflammatory feedback, and the numerical simulation of delayed stochastic biological systems. A limitation of the present study is that the model uses aggregated biological variables and does not explicitly distinguish individual cytokines, adhesion molecules, or immune-cell subpopulations. In addition, the model does not separately represent the acute, subacute, and convalescent clinical phases of Kawasaki disease, nor does it include coronary artery inflammation as an independent state variable. Future work may extend the model by including phase-dependent parameters, coronary artery involvement, immune-cell recruitment, and multiple biological delays.

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Author Contributions: The authors confirm their contributions to the paper as follows: Ali Raza: Conceptualization, mathematical modeling, stochastic formulation, delay differential analysis, computational implementation, data collection, data analysis, theoretical validation, model refinement, interpretation of results, interpretation of epidemiological aspects, visualization, literature review, validation, supervision, project administration, writing—original draft, and

writing—review & editing. Umar Shafique: Visualization, literature review, and writing—original draft. Marek Lampart: Conceptualization, methodology, and writing—review & editing. Dumitru Baleanu: Model refinement and validation. Hadil Alhazmi: Funding acquisition and visualization. Emad Fadhal: Validation and funding acquisition. All authors reviewed and approved the final version of the manuscript.

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Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

KD	Kawasaki Disease
VEGF	Vascular Endothelial Growth Factor
DDE	Delay Differential Equation
SDE	Stochastic Differential Equation
NSFD	Nonstandard Finite Difference
SNSFD	Stochastic Nonstandard Finite Difference

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