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A STOCHASTIC MULTI-SCALE COVID-19 MODEL WITH INTERVAL PARAMETERS*

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Abstract A stochastic multi-scale COVID-19 model that coupling within-host and between-host dynamics with interval parameters is established. The model is composed of a within-host fast model and a between-host slow stochastic model. The dynamics of fast model can be governed by basic reproduction number R_{0w}. The uninfected equilibrium E_{0w} is globally asymptotically stable (g.a.s) when $R_{0w} < 1$, but infected equilibrium E^*_{fast} is g.a.s when $R_{0w} > 1$. The dynamics of the coupling slow stochastic model can be governed by stochastic threshold R_s. The disease will die out when $R_s < 1$ and will persistent in mean when $R_s > 1$. One finds that R_s is an increasing function of R_{0w}. Further, some numerical simulations are presented to demonstrate the results and reveal that the dynamics of the slow stochastic model are approximate to the stochastic multi-scale model. It provides us a method to investigate the stochastic multi-scale model. Furthermore, some effective measures are given to control the COVID-19. Moreover, our work contributes basic understandings of coupling within-host and between-host models with interval parameters and environmental noises.

Keywords COVID-19, stochastic multi-scale, interval parameter, stochastic threshold, persistence in mean.

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1. Introduction

In March 2020, a novel coronavirus disease (COVID-19) was declared as a major global health threat by World Health Organization(WHO). As of 2 August 2023, have been 768983095 confirmed cases of COVID-19 including 6953743 deaths reported to the WHO [42]. Epidemic models are useful for us to understand infectious disease dynamics and develop preventive measures [20, 22, 35, 38, 47]. At microscale scale, many models about COVID-19 have been proposed [1, 24]. For instance, the authors in [24] investigate the within-host viral dynamics of COVID-19 of the model

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as follows

$$\begin{cases} \frac{\mathrm{d}E_p(s)}{\mathrm{d}s} &= d_p(E_p(0) - E_p(s)) - \beta_w E_p(s)V(s), \\ \frac{\mathrm{d}E_{p\nu}(s)}{\mathrm{d}s} &= \beta_w E_p(s)V(s) - d_{p\nu}E_{p\nu}(s), \\ \frac{\mathrm{d}V(s)}{\mathrm{d}s} &= \pi_\nu E_{p\nu}(s) - d_\nu V(s), \end{cases} \tag{1.1}$$

where E_p, $E_{p\nu}$ and V are the number of uninfected pulmonary epithelial cells, infected pulmonary epithelial cells and the virus. They obtain a basic reproductive number $R_{01w} = \frac{\beta_w \pi_\nu E_p(0)}{d_{p\nu} d_\nu}$ of the within-host scale model (1.1). At macroscale scale, a lot of mathematical models of COVID-19 have been studied [21,28,34,44]. The authors investigate the between-host transmission dynamics of COVID-19 and give effective control measures. Obviously, when a person infected with COVID-19 is found, he should be quarantined. It should be noted that the people who have recovered from COVID-19 can also become infected again. SIQS epidemic model is an important model in diseases control [6,10,15,40]. For simplicity's sake, many researchers use SIQS model to investigate the COVID-19 [23,37].

The authors in [1,23,24,37] establish single scale models to investigate within-host virus dynamics at the individual level and provide some treatment measures, or explore between-host transmission dynamics at the group level. However, many studies have shown that viral load at an individual level can significantly affect the progression of infection [14,45]. The higher the viral load, the greater the between-host transmission rate. This means that the dynamics at different scales are not independent of each other, but closely related. Then, it is important to construct a multi-scale model that can combine within-host and between-host scales [13].

In recent years, some multi-scale models have been proposed in the area of mathematical biology [2,12,25,27,39]. They integrated the within-host model into the between-host model by introducing the viral load-dependent between-host transmission rate or disease-induced mortality rate to explore the potential effect of micro dynamics on the macro dynamics. In 2012, Feng et al. [12] investigated a model for coupling within-host and between-host dynamics in an infectious disease. They further showed that the two dynamic processes are explicitly depend on each other. In 2018, Almocera et al. [2] mainly studied that the basic reproduction number for between-host dynamics is an increasing function of the basic reproduction number for within-host dynamics. In 2021, Li et al. [25] researched a two-strain model with coinfection that links immunological and epidemiological dynamics across scales. In 2022, Wang et al. [39] investigated a multi-scale model of COVID-19 for coupling within-host and between-host dynamics. They showed that immune response play a significant role in controlling viral replication within infected individuals. In 2023, Liu et al. [27] presented a coupled model linking the evolutionary dynamics of viral virulence to transmission dynamics in order to investigate the influence of evolutionary dynamics on transmission dynamics. However, the multi-scale models [2,12,25,27,39] are deterministic. Many studies have shown that environmental noises have a significant impact on the development of epidemic [30]. Stochastic epidemic models are more appropriate to investigate epidemic model in many circumstances [18,33,41]. To the best of our knowledge, there are very few studies of stochastic epidemic models that coupling within-host viral dynamics and between-host transmission dynamics under environmental noises. It is very difficult to investigate stochastic multi-scale epidemic model that coupling within-host and between-host dynamics, since it requires data from within-host and between-host for the same individual. Inspired by [39], one uses a conceptual "average" individual to avoid the complexity of keeping track of the dynamics within each individual. The within-host dynamics usually occur on the time scale of hours to days, which corresponding to fast dynamics. However, the between-host transmission dynamics occur on the scale of weeks, months to years, which corresponding to slow dynamics.

Inspired by the above discussions, one establishes a stochastic multi-scale model of slow-fast system which coupling within-host and between-host dynamics with precise parameters as follows:

$$\begin{cases} \mathrm{d}S(t) = \Big\{\Lambda - \psi_0(S,I) - \mu S + \gamma I + \varepsilon Q\Big\}\mathrm{d}t + \sigma_1 S\mathrm{d}B_1(t), \\ \mathrm{d}I(t) = \Big\{\psi_0(S,I) - \Big[\mu + \omega_2 + \delta + \gamma\Big]I\Big\}\mathrm{d}t + \sigma_2 I\mathrm{d}B_2(t), \\ \mathrm{d}Q(t) = \Big\{\delta I - \Big[\mu + \omega_3 + \varepsilon\Big]Q\Big\}\mathrm{d}t + \sigma_3 Q\mathrm{d}B_3(t), \\ \mathrm{d}E_p(t) = \frac{1}{\epsilon}\Big[d_p(E_p(0) - E_p) - \beta_w E_p V\Big]\mathrm{d}t, \\ \mathrm{d}E_{p\nu}(t) = \frac{1}{\epsilon}\Big[\beta_w E_p V - d_{p\nu}E_{p\nu}\Big]\mathrm{d}t, \\ \mathrm{d}V(t) = \frac{1}{\epsilon}\Big[\pi_\nu E_{p\nu} - d_\nu V\Big]\mathrm{d}t, \end{cases}$$

where S, I and Q are the number of susceptible, infective and quarantined individuals, respectively. $0 < \epsilon \ll 1$ is a small dimensionless parameter. $B_i(t)\,(i = 1,\,2,\,3)$ are standard one-dimensional independent Brownian motions with intensity $\sigma_i > 0\,(i = 1,\,2,\,3)$. Considering inhibition effect of susceptible individuals and infectives individuals, one chooses the incidence rate of the Crowley-Martin type as

$$\psi_0(S,I) = \frac{\beta_0(V)SI}{1 + \alpha_1 S + \alpha_2 I + \alpha_1\alpha_2 SI},$$

where α_1 represent the measure of inhibition effect, such as preventive measure taken by susceptible individuals, α_2 represent the measure of inhibition effect such as treatment with respect to infectives [8, 11]. $\beta_0(V) = \frac{rV}{K_w V+1}$ is the coupling function of the viral load [45].

Further, the parameters of the models [2, 12, 25, 27, 39] are assumed to be precisely known. However, parameters of model may be imprecise due to the lack of the accurate information data or the errors in the measurements. Therefore, epidemic models with imprecise parameters must be considered [3, 4]. Fortunately, the imprecise parameter can be expressed by interval number [9]. For instance, let $\hat{\Lambda}$ represents the corresponding imprecise parameter of Λ. $\hat{\Lambda}$ can be expressed by interval number $\hat{\Lambda} = [\Lambda^l, \Lambda^u]$, where Λ^l and Λ^u are the lower and upper limit of the interval number $\hat{\Lambda}$, respectively. Meanwhile, interval number can be expressed by interval-valued function [9]. Hence, $\hat{\Lambda} = (\Lambda^l)^{1-k}(\Lambda^u)^k$, $k \in [0, 1]$. Similarly, imprecise parameters of other parameters can be represented by interval parametric function. Therefore, one obtains a stochastic multi-scale model which coupling within-host and between-host dynamics with interval parameters as follows:

$$\begin{cases} \mathrm{d}S(t) = \Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \psi_1(S,I) - (\mu^l)^{1-k}(\mu^u)^k S + (\gamma^l)^{1-k}(\gamma^u)^k I \\ \qquad\qquad +(\varepsilon^l)^{1-k}(\varepsilon^u)^k Q\Big\}\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1(t), \\ \mathrm{d}I(t) = \Big\{\psi_1(S,I) - A_1 I\Big\}\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2(t), \\ \mathrm{d}Q(t) = \Big\{(\delta^l)^{1-k}(\delta^u)^k I - A_2 Q\Big\}\mathrm{d}t + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3(t), \\ \mathrm{d}E_p(t) = \frac{1}{\epsilon}\Big[(d_p^l)^{1-k}(d_p^u)^k(E_p(0) - E_p) - (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V\Big]\mathrm{d}t, \\ \mathrm{d}E_{p\nu}(t) = \frac{1}{\epsilon}\Big[(\beta_w^l)^{1-k}(\beta_w^u)^k E_p V - (d_{p\nu}^l)^{1-k}(d_{p\nu}^u)^k E_{p\nu}\Big]\mathrm{d}t, \\ \mathrm{d}V(t) = \frac{1}{\epsilon}\Big[(\pi_\nu^l)^{1-k}(\pi_\nu^u)^k E_{p\nu} - (d_\nu^l)^{1-k}(d_\nu^u)^k V\Big]\mathrm{d}t, \end{cases} \tag{1.2}$$

where

$$\begin{aligned} \psi_1(S,I) &= \frac{\beta(V)SI}{1 + (\alpha_1^l)^{1-k}(\alpha_1^u)^k S + (\alpha_2^l)^{1-k}(\alpha_2^u)^k I + (\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k SI}, \\ A_1 &= (\mu^l)^{1-k}(\mu^u)^k + (\omega_2^l)^{1-k}(\omega_2^u)^k + (\delta^l)^{1-k}(\delta^u)^k + (\gamma^l)^{1-k}(\gamma^u)^k, \\ A_2 &= (\mu^l)^{1-k}(\mu^u)^k + (\omega_3^l)^{1-k}(\omega_3^u)^k + (\varepsilon^l)^{1-k}(\varepsilon^u)^k, \end{aligned} \tag{1.3}$$

with $\beta(V) = \frac{(r^l)^{1-k}(r^u)^k V}{(K_w^l)^{1-k}(K_w^u)^k V+1}$ and parameter imprecision $k \in [0,1]$. The description of the model's parameters are shown in Table 1.

This paper is organized as follows. In Section 2, one presents several preliminaries. In Section 3, stability and bifurcation of the fast model of multi-scale model (1.2) are given. In Section 4, dynamics of slow stochastic model of multi-scale model (1.2) are investigated. In Section 5, some numerical simulations are presented. In Section 6, some conclusions and suggestions are given.

2. Preliminaries

In this section, one gives several preliminaries in the following. Let $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ be a complete probability space with the filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual conditions. $B_i(t)$ $(i = 1,\ 2,\ 3)$ are $\mathcal{F}_t$-adapted defined on the complete probability space. Let $\mathbb{R}_+^3 := \{(X_1, X_2, X_3) : X_i > 0, i = 1,\ 2,\ 3\}$.

Consider a 3-dimensional stochastic differential equation as follows:

$$\mathrm{d}X(t) = f(X(t),t)\mathrm{d}t + g(X(t),t)\mathrm{d}B(t), \quad t \geq 0, \tag{2.1}$$

with initial value $X(0) = X_0 \in \mathbb{R}_+^3$, where $B(t)$ is a standard 3-dimensional Brownian motion. An operator $\mathcal{L}$ related to equation (2.1) is defined by [29],

$$\mathcal{L} = \frac{\partial}{\partial t} + \sum_{i=1}^{3} f_i(X,t)\frac{\partial}{\partial X_i} + \frac{1}{2}\sum_{i,j=1}^{3}\Big[g^\top(X,t)g(X,t)\Big]_{ij}\frac{\partial^2}{\partial X_i \partial X_j}.$$

By operating $\mathcal{L}$ on $\mathrm{V}(x,t)$ (functions from space $C^{2,1}(\mathbb{R}_+^3 \times [t_0,\infty), \mathbb{R}_+)$, one has

$$\mathcal{L}\mathrm{V}(X,t) = \mathrm{V}_t(X,t) + \mathrm{V}_X(X,t)f(X,t) + \frac{1}{2}\mathrm{trac}\Big[g^\top(X,t)\mathrm{V}_{XX}(X,t)g(X,t)\Big],$$

where $(\cdot)^\top$ is the transpose and

$$\mathrm{V}_t = \frac{\partial \mathrm{V}}{\partial t},\ \mathrm{V}_X = \Big(\frac{\partial \mathrm{V}}{\partial X_1}, \frac{\partial \mathrm{V}}{\partial X_2}, \frac{\partial \mathrm{V}}{\partial X_3}\Big)^\top,\ \mathrm{V}_{XX} = \Big(\frac{\partial^2 \mathrm{V}}{\partial X_i \partial X_j}\Big)_{3\times 3}.$$

Applying the Itô's formula, one obtains

$$\mathrm{dV}(X(t),t) = \mathcal{L}\mathrm{V}(X(t),t)\mathrm{d}t + \mathrm{V}_X(X(t),t)g(X(t),t)\mathrm{d}B(t).$$

Definition 2.1. [9] (Interval number) An interval number $\mathbb{A}$ is denoted by a closed interval $[a^l, a^u]$ and defined by $\mathbb{A} = [a^l, a^u] = \{x | a^l \le x \le a^u, x \in \mathbb{R}\}$, where $\mathbb{R}$ is the set of real numbers. a^l and a^u are the lower and upper limit of the interval number, respectively. Especially, every real number can be denoted by the interval number $[a, a]$.

For any two interval numbers $\mathbb{A} = [a^l, a^u]$ and $\mathbb{B} = [b^l, b^u]$, one defines the following arithmetic operations

(i) Addition: $\mathbb{A} + \mathbb{B} = [a^l, a^u] + [b^l, b^u] = [a^l + b^l, a^u + b^u]$;

(ii) Subtraction: $\mathbb{A} - \mathbb{B} = [a^l, a^u] - [b^l, b^u] = [a^l - b^u, a^u - b^l]$;

(iii) Scalar multiplication:

$$\alpha\mathbb{A} = \alpha[a^l, a^u] = \begin{cases} [\alpha a^l, \alpha a^u], & \text{if } \ \alpha \ge 0, \\ [\alpha a^u, \alpha a^l], & \text{if } \ \alpha < 0. \end{cases}$$

(iv) Multiplication:
$\mathbb{A} \cdot \mathbb{B} = [a^l, a^u] \cdot [b^l, b^u] = \big[\min\{a^l b^l, a^l b^u, a^u b^l, a^l b^u\}, \max\{a^l b^l, a^l b^u, a^u b^l, a^l b^u\}\big]$;

(v) Division: $\mathbb{A}/\mathbb{B} = [a^l, a^u]/[b^l, b^u] = [a^l, a^u] \cdot [\frac{1}{b^u}, \frac{1}{b^l}]$.

Definition 2.2. [9] (Interval-valued function) An interval-valued function for the interval $[a^l, a^u]$ can be represented by a function $h(k) = (a^l)^{1-k}(a^u)^k$ for $k \in [0, 1]$.

Definition 2.3. [5] (Stochastically ultimate boundedness) The solution $X(t)$ of (2.1) is called to be stochastically ultimately bounded, if for any $\xi \in (0, 1)$, there is a positive constant $\rho = \rho(\xi)$, such that

$$\limsup_{t\to\infty} \mathbb{P}[|X(t)| > \rho] < \xi.$$

Definition 2.4. [5] (Stochastic permanence) The solution $X(t)$ of (2.1) is called to be stochastically permanence, if for any $\xi \in (0, 1)$, there is a pair of positive constants $\rho = \rho(\xi)$ and $\varrho = \varrho(\xi)$ such that

$$\liminf_{t\to\infty} \mathbb{P}[|X(t)| \le \rho] \ge 1 - \xi,\ \liminf_{t\to\infty} \mathbb{P}[|X(t)| \ge \varrho] \ge 1 - \xi.$$

Definition 2.5. [26] (Persistence in mean) The solution $X(t)$ of (2.1) is called persistence in mean, if there exists a positive constant m such that

$$\liminf_{t\to\infty} \langle X(t) \rangle > m > 0,\ a.s. \ \text{ where, } \langle X(t) \rangle = \frac{1}{t}\int_0^t X(s)\mathrm{d}s.$$

3. Stability and bifurcation of fast model of (1.2)

This section investigates the stability and bifurcation of the fast model of multi-scale model (1.2). In the fast time scale $\tau = \frac{t}{\epsilon}$, the multi-scale model (1.2) can be written as

$$\begin{cases} \mathrm{d}S(\tau) = \epsilon\Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \psi_1(S,I) - (\mu^l)^{1-k}(\mu^u)^k S + (\gamma^l)^{1-k}(\gamma^u)^k I \\ \qquad\qquad +(\varepsilon^l)^{1-k}(\varepsilon^u)^k Q\Big\}\mathrm{d}\tau + \sqrt{\epsilon}(\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1(\tau), \\ \mathrm{d}I(\tau) = \epsilon\Big\{\psi_1(S,I) - A_1 I\Big\}\mathrm{d}\tau + \sqrt{\epsilon}(\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2(\tau), \\ \mathrm{d}Q(\tau) = \epsilon\Big\{(\delta^l)^{1-k}(\delta^u)^k I - A_2 Q\Big\}\mathrm{d}\tau + \sqrt{\epsilon}(\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3(\tau), \\ \mathrm{d}E_p(\tau) = \Big[(d_p^l)^{1-k}(d_p^u)^k(E_p(0) - E_p) - (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V\Big]\mathrm{d}\tau, \\ \mathrm{d}E_{p\nu}(\tau) = \Big[(\beta_w^l)^{1-k}(\beta_w^u)^k E_p V - (d_{p\nu}^l)^{1-k}(d_{p\nu}^u)^k E_{p\nu}\Big]\mathrm{d}\tau, \\ \mathrm{d}V(\tau) = \Big[(\pi_\nu^l)^{1-k}(\pi_\nu^u)^k E_{p\nu} - (d_\nu^l)^{1-k}(d_\nu^u)^k V\Big]\mathrm{d}\tau. \end{cases}$$

Let $\epsilon \to 0$ yields,

$$\begin{cases} \frac{\mathrm{d}E_p(\tau)}{\mathrm{d}\tau} = (d_p^l)^{1-k}(d_p^u)^k(E_p(0) - E_p) - (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V, \\ \frac{\mathrm{d}E_{p\nu}(\tau)}{\mathrm{d}\tau} = (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V - (d_{p\nu}^l)^{1-k}(d_{p\nu}^u)^k E_{p\nu}, \\ \frac{\mathrm{d}V(\tau)}{\mathrm{d}\tau} = (\pi_\nu^l)^{1-k}(\pi_\nu^u)^k E_{p\nu} - (d_\nu^l)^{1-k}(d_\nu^u)^k V. \end{cases} \tag{3.1}$$

Obviously, the within-host fast model (3.1) has an uninfected equilibrium $E_{0fast} = (E_p(0), 0, 0)$. By the method of next generation matrix [36], the basic reproductive number of the fast model (3.1) is

$$R_{0w} = \frac{(\beta_w^l \pi_\nu^l)^{1-k}(\beta_w^u \pi_\nu^u)^k E_p(0)}{(d_{p\nu}^l d_\nu^l)^{1-k}(d_{p\nu}^u d_\nu^u)^k}. \tag{3.2}$$

Further, if $R_{0w} > 1$, the model (3.1) has an infected equilibrium $E^*_{fast} = (E_p^*, E_{p\nu}^*, V^*)$, where

$$E_p^* = \frac{E_p(0)}{R_{0w}},\ E_{p\nu}^* = \frac{(d_p^l d_\nu^l)^{1-k}(d_p^u d_\nu^u)^k}{(\beta_w^l \pi_\nu^l)^{1-k}(\beta_w^u \pi_\nu^u)^k}(R_{0w} - 1),\ V^* = \frac{(d_p^l)^{1-k}(d_p^u)^k}{(\beta_w^l)^{1-k}(\beta_w^u)^k}(R_{0w} - 1). \tag{3.3}$$

Theorem 3.1. *The uninfected equilibrium E_{0fast} of the deterministic fast model (3.1) is globally asymptotically stable if $R_{0w} < 1$.*

Proof. Define a Lyapunov function

$$L_1 = \frac{(\pi_\nu^l)^{1-k}(\pi_\nu^u)^k}{(d_{p\nu}^l)^{1-k}(d_{p\nu}^u)^k} E_{p\nu} + V.$$

It follows that

$$\frac{\mathrm{d}L_1}{\mathrm{d}\tau} = (d_\nu^l)^{1-k}(d_\nu^u)^k\left[\frac{(\beta_w^l \pi_\nu^l)^{1-k}(\beta_w^u \pi_\nu^u)^k E_p}{(d_{p\nu}^l d_\nu^l)^{1-k}(d_{p\nu}^u d_\nu^u)^k} - 1\right] V \le (d_\nu^l)^{1-k}(d_\nu^u)^k(R_{0w} - 1)V.$$

Obviously, when $R_{0w} < 1$, $\frac{\mathrm{d}L_1}{\mathrm{d}\tau} < 0$. When $V = 0$, then $\frac{\mathrm{d}L_1}{\mathrm{d}\tau} = 0$. By the LaSalle's Invariance Principle, E_{0fast} is globally asymptotically stable if $R_{0w} < 1$. □

Theorem 3.2. *The infected equilibrium E^*_{fast} of the model (3.1) is globally asymptotically stable if $R_{0w} > 1$.*

Proof. The proof of this theorem is similar to [31], so one omits it. □

Theorem 3.3. *Suppose the infection rate of virus is $\beta^l_w = \beta^u_w = \beta_w$. When β_w crosses β^*_w from below, the model (3.1) undergoes forward bifurcation at $R_{0w} = 1$, where*

$$\beta^*_w = \frac{(d^l_{p\nu} d^l_\nu)^{1-k}(d^u_{p\nu} d^u_\nu)^k}{(\pi^l_\nu)^{1-k}(\pi^u_\nu)^k E_p(0)}. \tag{3.4}$$

Proof. It follows from $R_{0w} = 1$ that (3.4) holds. Let $Y = (y_1, y_2, y_3)^\top = (E_p, E_{p\nu}, V)^\top$. Hence, the model (3.1) can be written as $\dot{Y} = (g_1, g_2, g_3)^\top$. The Jacobian matrix of the model (3.1) at the disease-free E_{0fast} is given by

$$J(E_{0fast}) = \begin{bmatrix} -(d^l_p)^{1-k}(d^u_p)^k & 0 & -\beta_w E_p(0) \\ 0 & -(d^l_{p\nu})^{1-k}(d^u_{p\nu})^k & \beta_w E_p(0) \\ 0 & (\pi^l_\nu)^{1-k}(\pi^u_\nu)^k & -(d^l_\nu)^{1-k}(d^u_\nu)^k \end{bmatrix}.$$

Hence, one obtains the characteristic polynomial of $J(E_{0fast})$ as follows

$$\begin{aligned} f(\lambda) = &- (\lambda + (d^l_p)^{1-k}(d^u_p)^k)\Big[(\lambda + (d^l_{p\nu})^{1-k}(d^u_{p\nu})^k)(\lambda + (d^l_\nu)^{1-k}(d^u_\nu)^k) \\ &- \beta_w (\pi^l_\nu)^{1-k}(\pi^u_\nu)^k E_p(0)\Big]. \end{aligned}$$

The Jacobian $J(E_{0fast})$ at $\beta_w = \beta^*_w$ has eigenvalues

$$\lambda_1 = -(d^l_p)^{1-k}(d^u_p)^k,\ \lambda_2 = 0,\ \lambda_3 = -(d^l_{p\nu})^{1-k}(d^u_{p\nu})^k - (d^l_\nu)^{1-k}(d^u_\nu)^k,$$

then E_{0fast} is the non-hyperbolic equilibrium point. Let $\nu = (\nu_1, \nu_2, \nu_3)^\top$ and $w = (w_1, w_2, w_3)^\top$ represent the left and right eigenvectors corresponding to the eigenvalue zero of $J(E_{0fast}, \beta^*_w)$, respectively. Hence, one can calculate that

$$\begin{aligned} &\nu_1 = 0,\ \nu_2 = 1,\ \nu_3 = \frac{\beta^*_w E_p(0)}{(d^l_\nu)^{1-k}(d^u_\nu)^k},\ w_1 = \beta^*_w E_p(0), \\ &w_2 = \frac{(d^l_p d^l_\nu)^{1-k}(d^u_p d^u_\nu)^k}{(\pi^l_\nu)^{1-k}(\pi^u_\nu)^k},\ w_3 = \frac{\beta^*_w E_p(0)(d^l_p)^{1-k}(d^u_p)^k}{(d^l_{p\nu})^{1-k}(d^u_{p\nu})^k}. \end{aligned}$$

According to the Theorem 4.1 in [7], the local dynamic behavior near $R_{0w} = 1$ can be determined by constants **a** and **b** in the following:

$$\mathbf{a} = \sum_{\kappa,i,j=1}^{3} \nu_\kappa w_i w_j \frac{\partial^2 g_\kappa}{\partial y_i \partial y_j}(E_{0fast}, \beta^*_w), \quad \mathbf{b} = \sum_{\kappa,i=1}^{3} \nu_\kappa w_i \frac{\partial^2 g_\kappa}{\partial y_i \partial \beta_w}(E_{0fast}, \beta^*_w).$$

In order to calculate **a** and **b**, one just to find the nonzero partial derivative of g_2 at $J(E_{0fast}, \beta^*_w)$, hence

$$\frac{\partial^2 g_2}{\partial y_1 \partial y_3}(E_{0fast}, \beta^*_w) = \frac{\partial^2 g_2}{\partial y_3 \partial y_1}(E_{0fast}, \beta^*_w) = \beta^*_w,\ \frac{\partial^2 g_2}{\partial y_3 \partial \beta_w}(E_{0fast}, \beta^*_w) = E_p(0).$$

It follows that

$$\mathbf{a} = -2(\beta_w^*)^2(\pi_\nu^l d_p^l)^{1-k}(\pi_\nu^u d_p^u)^k < 0,\ \mathbf{b} = (d_p^l)^{1-k}(d_p^u)^k E_p(0) > 0.$$

By the Theorem 4.1 in [7], model (3.1) has forward bifurcation at $R_{0w} = 1$. □

Remark 3.1. As R_{0w} crosses 1, E_{0fast} changes its stability from stable to unstable and a globally asymptotically infected equilibrium E^*_{fast} appears.

4. Dynamics of slow stochastic model of (1.2)

This section investigates the dynamics of the following slow stochastic model (4.1) of multi-scale model (1.2). In the slow time scale $t = \epsilon\tau$, the within-host dynamics of multi-scale model (1.2) can be rewritten as

$$\begin{cases} \epsilon\frac{\mathrm{d}E_p(t)}{\mathrm{d}t} &= (d_p^l)^{1-k}(d_p^u)^k(E_p(0) - E_p) - (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V, \\ \epsilon\frac{\mathrm{d}E_{p\nu}(t)}{\mathrm{d}t} &= (\beta_w^l)^{1-k}(\beta_w^u)^k E_p V - (d_{p\nu}^l)^{1-k}(d_{p\nu}^u)^k E_{p\nu}, \\ \epsilon\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= (\pi_\nu^l)^{1-k}(\pi_\nu^u)^k E_{p\nu} - (d_\nu^l)^{1-k}(d_\nu^u)^k V. \end{cases}$$

Letting $\epsilon = 0$, it leads to (3.3). When $R_{0w} < 1$, the virus $V(t)$ dies out quickly, then $\beta(V) = 0$ of multi-scale model (1.2). It follows that

$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} Q(t) = 0.$$

When $R_{0w} > 1$, $V(t)$ will quickly stabilize to V^* which is shown in (3.3). Thus, one takes V^* replaces $V(t)$ in the model (1.2). Therefore, one obtains a between-host slow stochastic model as follows:

$$\begin{cases} \mathrm{d}S(t) &= \Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \psi(S,I) - (\mu^l)^{1-k}(\mu^u)^k S + (\gamma^l)^{1-k}(\gamma^u)^k I \\ &\qquad + (\varepsilon^l)^{1-k}(\varepsilon^u)^k Q\Big\}\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1(t), \\ \mathrm{d}I(t) &= \{\psi(S,I) - A_1 I\}\,\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2(t), \\ \mathrm{d}Q(t) &= \Big\{(\delta^l)^{1-k}(\delta^u)^k I - A_2 Q\Big\}\mathrm{d}t + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3(t), \end{cases} \tag{4.1}$$

where

$$\psi(S,I) = \frac{\beta(V^*)SI}{1 + (\alpha_1^l)^{1-k}(\alpha_1^u)^k S + (\alpha_2^l)^{1-k}(\alpha_2^u)^k I + (\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k SI},$$

with $\beta(V^*) = \frac{(r^l)^{1-k}(r^u)^k V^*}{(K_w^l)^{1-k}(K_w^u)^k V^* + 1}$.

4.1. Stability of the slow deterministic model (4.1)

When noise intensity $(\sigma_i^l)^{1-k}(\sigma_i^u)^k = 0, (i = 1,2,3)$, the stochastic model (4.1) become a deterministic model. Obviously, the disease-free equilibrium of the deterministic model of model (4.1) is $E_0 = \Big(\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}, 0, 0\Big)$. The basic reproduction number of the deterministic model (4.1) is

$$R_{0b} = \frac{\beta(V^*)(\Lambda^l)^{1-k}(\Lambda^u)^k}{\Big[(\mu^l)^{1-k}(\mu^u)^k + (\alpha_1^l\Lambda^l)^{1-k}(\alpha_1^u\Lambda^u)^k\Big]A_1}, \tag{4.2}$$

where A_1 is given in (1.3).

Theorem 4.1. *The disease-free equilibrium E_0 of the deterministic model (4.1) is globally asymptotically stable if $R_{0b} < 1$.*

Proof. Let $N(t) = S(t) + I(t) + Q(t)$, one has

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = (\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k N - (\omega_2^l)^{1-k}(\omega_2^u)^k I - (\omega_3^l)^{1-k}(\omega_3^u)^k Q.$$

It leads to

$$\limsup_{t\to\infty} N(t) \le \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}.$$

Consider the Liapunov function $L_2 = I$, it follows that

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t} &= \left\{\frac{\beta(V^*)S}{\Phi} - A_1\right\} I \\ &\le \left\{\frac{\beta(V^*)(\Lambda^l)^{1-k}(\Lambda^u)^k}{[(\mu^l)^{1-k}(\mu^u)^k + (\alpha_1^l\Lambda^l)^{1-k}(\alpha_1^u\Lambda^u)^k]} - A_1\right\} I \\ &= A_1(R_{0b} - 1)I,\end{aligned}$$

where

$$\Phi = 1 + (\alpha_1^l)^{1-k}(\alpha_1^u)^k S + (\alpha_2^l)^{1-k}(\alpha_2^u)^k I + (\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k SI. \tag{4.3}$$

Obviously, when $R_{0b} < 1$, $\frac{\mathrm{d}L_2}{\mathrm{d}t} < 0$. $\frac{\mathrm{d}L_2}{\mathrm{d}t} = 0$, iff $I = 0$. Meanwhile, it leads to $Q \to 0$ and $S \to \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}$. According to the LaSalle's Invariance Principle, E_0 is globally asymptotically stable if $R_{0b} < 1$. □

Remark 4.1. The large inhibition effect $[\alpha_1^l, \alpha_1^u]$ of S can lead the basic reproduction number R_{0b} small. When the parameters are precise and $\beta(V^*) = \beta$, the basic reproduction number R_{0b} degrades to the basic reproduction number R_0 which has been investigated in [15].

4.2. Existence and uniqueness of positive solution of (4.1)

This subsection investigates the existence and uniqueness of positive solution of (4.1) of multi-scale model (1.2).

Theorem 4.2. *For any given initial value $(S(0), I(0), Q(0)) \in \mathbb{R}_+^3$, the model (4.1) has a unique positive solution $(S(t), I(t), Q(t))$ and it stays in $\mathbb{R}_+^3$ with probability one for all $t \ge 0$.*

Proof. Because the coefficients of the stochastic model (4.1) are locally Lipschitz continuous, then the model (4.1) has a unique local solution $(S(t), I(t), Q(t))$ for $0 \le t < \tau_e$, where τ_e be the explosion time. In order to prove the globality of the solution, one will proof $\tau_e = \infty$ a.s. One chooses $n_0 > 0$ large enough such that $S(0) > 0$, $I(0) > 0$ and $Q(0) > 0$ in the interval $[\frac{1}{n_0}, n_0]$. For any $n > n_0$, defining a stop-time

$$\tau_n = \inf\left\{t \in [0, \tau_e) : \min\{S, I, Q\} \le \frac{1}{n} \text{ or } \max\{S, I, Q\} \ge n\right\}.$$

Let $\inf \emptyset = \infty$ ($\emptyset$ denotes the empty set). Obviously, τ_n is increases as $n \to \infty$. Set $\tau_\infty = \lim_{n\to\infty} \tau_n$, hence $\tau_\infty \le \tau_e$. If one can demonstrate $\tau_\infty = \infty$, it means that $\tau_e = \infty$. Assuming $\tau_\infty \neq \infty$, then there are two positive constants T_1 and $0 < \eta < 1$ such that $\mathbb{P}\{\tau_\infty \le T_1\} \ge \eta$. Therefore, for each integer $n_1 \ge n_0$, one can obtain

$$\mathbb{P}[\tau_n \le T_1] \ge \eta, \; n \ge n_1.$$

Define a Liapunov function

$$\mathrm{V}_1(S, I, Q) = \Big(S - a - a\ln\frac{S}{a}\Big) + \Big(I - 1 - \ln I\Big) + \Big(Q - 1 - \ln Q\Big).$$

By the Itô's formula, one has

$$\begin{aligned}
&\mathrm{dV}_1 \\
=&\Big(1-\frac{a}{S}\Big)\Big\{\Big[(\Lambda^l)^{1-k}(\Lambda^u)^k - \frac{\beta(V^*)SI}{\Phi} - (\mu^l)^{1-k}(\mu^u)^k S + (\gamma^l)^{1-k}(\gamma^u)^k I \\
&+ (\varepsilon^l)^{1-k}(\varepsilon^u)^k Q\Big]\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1\Big\} + \frac{a(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}}{2}\mathrm{d}t \\
&+ \Big(1-\frac{1}{I}\Big)\Big\{\Big[\frac{\beta(V^*)SI}{\Phi} - A_1 I\Big]\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2\Big\} \\
&+ \Big(1-\frac{1}{Q}\Big)\Big\{\Big[(\delta^l)^{1-k}(\delta^u)^k I - A_2 Q\Big]\mathrm{d}t + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3\Big\} \\
&+ \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2}\mathrm{d}t + \frac{(\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}}{2}\mathrm{d}t \\
=&\Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k(S+I+Q) - (\omega_2^l)^{1-k}(\omega_2^u)^k I - (\omega_3^l)^{1-k}(\omega_3^u)^k Q \\
&- \frac{a(\Lambda^l)^{1-k}(\Lambda^u)^k}{S} + \frac{a\beta(V^*)I}{\Phi} + a(\mu^l)^{1-k}(\mu^u)^k - \frac{a(\gamma^l)^{1-k}(\gamma^u)^k I}{S} + A_1 + A_2 \\
&- \frac{a(\varepsilon^l)^{1-k}(\varepsilon^u)^k Q}{S} - \frac{\beta(V^*)S}{\Phi} - \frac{(\delta^l)^{1-k}(\delta^u)^k I}{Q} + \frac{a(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}}{2} \\
&+ \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} + \frac{(\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}}{2}\Big\}\mathrm{d}t + \Big(1-\frac{a}{S}\Big)(\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1 \\
&+ \Big(1-\frac{1}{I}\Big)(\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2 + \Big(1-\frac{1}{Q}\Big)(\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3.
\end{aligned}$$

Obviously, $\frac{\beta(V^*)I}{\Phi} \le (r^l)^{1-k}(r^u)^k I$. Let $a = \frac{(\omega_2^l)^{1-k}(\omega_2^u)^k}{(r^l)^{1-k}(r^u)^k}$, it follows that

$$\begin{aligned}
\mathrm{dV}_1 \le& K_1\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k(S-a)\mathrm{d}B_1 \\
&+ (\sigma_2^l)^{1-k}(\sigma_2^u)^k(I-1)\mathrm{d}B_2 + (\sigma_3^l)^{1-k}(\sigma_3^u)^k(Q-1)\mathrm{d}B_3,
\end{aligned}$$

where

$$\begin{aligned}
K_1 =& (\Lambda^l)^{1-k}(\Lambda^u)^k + a(\mu^l)^{1-k}(\mu^u)^k + A_1 + A_2 \\
&+ \frac{a(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}}{2} + \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} + \frac{(\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}}{2}.
\end{aligned}$$

The rest part of the proof is similar to [5]. □

4.3. Stochastically ultimately bounded and permanent

Theorem 4.3. *The solutions of model (4.1) are stochastically ultimately bounded and permanent for any initial value* $(S(0), I(0), Q(0)) \in \mathbb{R}^3_+$.

Proof. Let $N(t) = S(t) + I(t) + Q(t)$ and $\mathrm{V}_2(X(t)) = N + \frac{1}{N}$. Applying the Itô's formula, one has

$$
\begin{aligned}
\mathrm{dV}_2(X(t)) =& \Big(1 - \frac{1}{N^2}\Big)\Big\{\Big[(\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k N - (\omega_2^l)^{1-k}(\omega_2^u)^k I \\
& - (\omega_3^l)^{1-k}(\omega_3^u)^k Q\Big]\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1 + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2 \\
& + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3\Big\} + \frac{1}{N^3}\Big[(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}S^2 + (\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}I^2 \\
& + (\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}Q^2\Big]\mathrm{d}t \\
=& \Big[(\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k N - (\omega_2^l)^{1-k}(\omega_2^u)^k I - (\omega_3^l)^{1-k}(\omega_3^u)^k Q \\
& - \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k N - (\omega_2^l)^{1-k}(\omega_2^u)^k I - (\omega_3^l)^{1-k}(\omega_3^u)^k Q}{N^2} \\
& + \frac{(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}S^2 + (\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}I^2 + (\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}Q^2}{N^3}\Big]\mathrm{d}t \\
& + \Big(1 - \frac{1}{N^2}\Big)\Big[(\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1 + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2 \\
& + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3\Big] \\
\le& \Big\{\frac{2(\mu^l)^{1-k}(\mu^u)^k + (\omega_2^l)^{1-k}(\omega_2^u)^k + (\omega_3^l)^{1-k}(\omega_3^u)^k + \sum_i^3(\sigma_i^l)^{1-k}(\sigma_i^u)^k}{N} \\
& -(\mu^l)^{1-k}(\mu^u)^k(N + \frac{1}{N}) + (\Lambda^l)^{1-k}(\Lambda^u)^k - \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{N^2}\Big\}\mathrm{d}t \\
& + \Big(1 - \frac{1}{N^2}\Big)\Big[(\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1 + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2 \\
& + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3\Big] \\
\le& \Big[K_2 - (\mu^l)^{1-k}(\mu^u)^k \mathrm{V}_2(t)\Big]\mathrm{d}t + \Big(1 - \frac{1}{N^2}\Big)\Big[(\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1 \\
& + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2 + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3\Big],
\end{aligned}
$$

where

$$
\begin{aligned}
K_2 =& \frac{\Big[2(\mu^l)^{1-k}(\mu^u)^k + (\omega_2^l)^{1-k}(\omega_2^u)^k + (\omega_3^l)^{1-k}(\omega_3^u)^k + \sum_i^3(\sigma_i^l)^{1-k}(\sigma_i^u)^k\Big]^2}{4(\Lambda^l)^{1-k}(\Lambda^u)^k} \\
& + (\Lambda^l)^{1-k}(\Lambda^u)^k.
\end{aligned}
$$

It follows that

$$
\begin{aligned}
\mathbb{E}[e^{(\mu^l)^{1-k}(\mu^u)^k t}\mathrm{V}_2(t)] =& \mathbb{E}[\mathrm{V}_2(0)] + \mathbb{E}\left[\int_0^t e^{(\mu^l)^{1-k}(\mu^u)^k s}[(\mu^l)^{1-k}(\mu^u)^k \mathrm{V}_2 + \mathcal{L}\mathrm{V}_2]\mathrm{d}s\right] \\
\le& \mathbb{E}[\mathrm{V}_2(0)] + K_2\mathbb{E}\left[\int_0^t e^{(\mu^l)^{1-k}(\mu^u)^k s}\mathrm{d}s\right]
\end{aligned}
$$

$$=\mathbb{E}[\mathrm{V}_2(0)] + \frac{K_2}{(\mu^l)^{1-k}(\mu^u)^k}\mathbb{E}\Big[e^{(\mu^l)^{1-k}(\mu^u)^k t} - 1\Big].$$

Hence,

$$\begin{aligned}\mathbb{E}[\mathrm{V}_2(t)] \leq& e^{-(\mu^l)^{1-k}(\mu^u)^k t}\mathbb{E}[\mathrm{V}(0)] + \frac{K_2}{(\mu^l)^{1-k}(\mu^u)^k}\mathbb{E}\Big[1 - e^{-(\mu^l)^{1-k}(\mu^u)^k t}\Big] \\ \leq& \mathbb{E}[\mathrm{V}_2(0)] + \frac{K_2}{(\mu^l)^{1-k}(\mu^u)^k} \\ :=& H.\end{aligned}$$

One chooses ρ sufficiently large such that $\frac{H}{\rho} < 1$. By Chebyshev's inequality,

$$\mathbb{P}\Big[N + \frac{1}{N} > \rho\Big] \leq \frac{1}{\rho}\mathbb{E}\Big[N + \frac{1}{N}\Big] \leq \frac{H}{\rho} := \xi.$$

Then,

$$1 - \xi \leq \mathbb{P}\Big[N + \frac{1}{N} \leq \rho\Big] \leq \mathbb{P}\Big[\frac{1}{\rho} \leq N \leq \rho\Big].$$

Since

$$N^2 \leq 3|X|^2 \leq 3N^2.$$

One gets

$$\mathbb{P}\left[\frac{1}{\sqrt{3}\rho} \leq \frac{N}{\sqrt{3}} \leq\mid X \mid\leq N \leq \rho\right] \geq 1 - \xi.$$

According to Definition 2.3 and Definition 2.4, the model (4.1) is stochastically ultimately bounded and permanent. □

Remark 4.2. The definition of stochastically permanent implies that the sum of all subpopulation of the model (4.1) is bounded above zero and below a certain number with probability arbitrary close to 1.

Next, one considers the region as follows:

$$\Gamma = \left\{(S, I, Q) \in \mathbb{R}^3_+ : S + I + Q \leq \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}\right\}.$$

Theorem 4.4. *The region Γ is almost surely positive invariant for the stochastic model (4.1).*

Proof. Let $X(0) \in \Gamma$, positive n_0 is sufficiently large such that $X(0)$ is contained within $\left(\frac{1}{n_0}, \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}\right]$. For each integer $n \geq n_0$, define the stopping times

$$\begin{aligned}\tau_n &= \inf\left\{t > 0 : X(t) \in \Gamma \ \text{ and } \ (S(t), I(t), Q(t)) \in \left(\frac{1}{n}, \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}\right]\right\}, \\ \tau &= \inf\Big\{t > 0 : X(t) \notin \Gamma\Big\}.\end{aligned}$$

It is sufficient to show that $\mathbb{P}[\tau = \infty] = 1$, equivalently, $\mathbb{P}[\tau < t] = 0$, $\forall t > 0$. It is easy to see that $\mathbb{P}[\tau < t] \leq \mathbb{P}[\tau_n < t]$. Hence, one only needs to prove that

$$\limsup_{n\to\infty} \mathbb{P}[\tau_n < t] = 0.$$

One chooses a C^2-function $\mathrm{V}_3 : \mathbb{R}^3_+ \to \mathbb{R}_+$

$$\mathrm{V}_3(X) = \frac{1}{S} + \frac{1}{I} + \frac{1}{Q}. \tag{4.4}$$

Applying Itô's formula on (4.4), one has

$$\begin{aligned}
&\mathrm{dV}_3(X(s)) \\
=& -\frac{1}{S^2}\Big\{\Big[(\Lambda^l)^{1-k}(\Lambda^u)^k - \frac{\beta(V^*)SI}{\Phi} - (\mu^l)^{1-k}(\mu^u)^k S + (\gamma^l)^{1-k}(\gamma^u)^k I \\
&+ (\varepsilon^l)^{1-k}(\varepsilon^u)^k Q\Big]\mathrm{d}s + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1(s)\Big\} \\
&- \frac{1}{I^2}\Big\{\Big[\frac{\beta(V^*)SI}{\Phi} - A_1 I\Big]\mathrm{d}s + (\sigma_2^l)^{1-k}(\sigma_2^u)^k I\mathrm{d}B_2(s)\Big\} \\
&- \frac{1}{Q^2}\Big\{\Big[(\delta^l)^{1-k}(\delta^u)^k I - A_2 Q\Big]\mathrm{d}s + (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q\mathrm{d}B_3(s)\Big\} \\
&+ \frac{(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}}{S}\mathrm{d}s + \frac{(\sigma_2^l)^{2-2k}(\sigma_1^u)^{2k}}{I}\mathrm{d}s + \frac{(\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}}{Q}\mathrm{d}s \\
\leq& \left[\frac{\beta(V^*)I}{\Phi} + (\mu^l)^{1-k}(\mu^u)^k + (\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}\right]\frac{1}{S}\mathrm{d}s - \frac{(\sigma_1^l)^{1-k}(\sigma_1^u)^k}{S}\mathrm{d}B_1(s) \\
&+ \Big[A_1 + (\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}\Big]\frac{1}{I}\mathrm{d}s + \Big[A_2 + (\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}\Big]\frac{1}{Q}\mathrm{d}s \\
&- \frac{(\sigma_2^l)^{1-k}(\sigma_2^u)^k}{I}\mathrm{d}B_2(s) - \frac{(\sigma_3^l)^{1-k}(\sigma_3^u)^k}{Q}\mathrm{d}B_3(s).
\end{aligned}$$

It follows that

$$\begin{aligned}
\mathrm{dV}_3(X(s)) \leq K_3\mathrm{V}_3(X(s))\mathrm{d}s - \tfrac{(\sigma_1^l)^{1-k}(\sigma_1^u)^k}{S}\mathrm{d}B_1(s) \\
-\tfrac{(\sigma_2^l)^{1-k}(\sigma_2^u)^k}{I}\mathrm{d}B_2(s) - \tfrac{(\sigma_3^l)^{1-k}(\sigma_3^u)^k}{Q}\mathrm{d}B_3(s).
\end{aligned} \tag{4.5}$$

where

$$\begin{aligned}
K_3 =& \max\Big\{\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k} + (\mu^l)^{1-k}(\mu^u)^k + (\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k}, \\
&A_1 + (\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}, A_2 + (\sigma_3^l)^{2-2k}(\sigma_3^u)^{2k}\Big\}.
\end{aligned}$$

Taking integral and expectation both sides of (4.5), using Fubini's theorem, one has

$$\mathbb{E}[\mathrm{V}_3(X(s))] \leq \mathrm{V}_3(X(0)) + K_3\int_0^s \mathbb{E}[\mathrm{V}_3(X(u))]\mathrm{d}u. \tag{4.6}$$

By Gronwall's inequality, (4.6) becomes

$$\mathbb{E}[\mathrm{V}_3(X(s))] \leq \mathrm{V}_3(X(0))e^{K_3 s},\ \forall s \in [0, t\wedge\tau_n].$$

Hence

$$\mathbb{E}[\mathrm{V}_3(X(t\wedge\tau_n))] \le \mathrm{V}_3(X(0))e^{K_3(t\wedge\tau_n)} \le \mathrm{V}_3(X(0))e^{K_3 t}, \forall t\ge 0. \tag{4.7}$$

Since $\mathrm{V}_3(X(t\wedge\tau_n))$ and some component of $X(\tau_n)$ is less than or equal to $\frac{1}{n}$

$$\mathbb{E}[\mathrm{V}_3(X(t\wedge\tau_n))] \ge \mathbb{E}[\mathrm{V}_3(X(\tau_n)\mathbb{I}_{\tau_n<t})] \ge n\mathbb{P}[\tau_n<t]. \tag{4.8}$$

It follows from (4.7) and (4.8), one obtains

$$\mathbb{P}[\tau_n<t] \le \frac{\mathrm{V}_3(X(0))e^{K_3 t}}{n}, \quad \forall t\ge 0.$$

Therefore,

$$\limsup_{n\to\infty} \mathbb{P}[\tau_n<t]=0, \quad \forall\, t\ge 0.$$

□

4.4. Extinction of the COVID-19

In order to control the COVID-19, one investigates the stochastic threshold of the model (4.1) of multi-scale model (1.2).

Lemma 4.1. [29] *Suppose that $M=\{M_t\}_{t\ge 0}$ be a real-valued continuous local martingle vanishing at $t=0$, then*

$$\lim_{t\to\infty}\langle M,M\rangle=\infty,\ a.s. \Rightarrow \lim_{t\to\infty}\frac{M_t}{\langle M,M\rangle}=0,\ a.s.,$$

and

$$\limsup_{t\to\infty}\frac{\langle M,M\rangle}{t}<\infty,\ a.s. \Rightarrow \lim_{t\to\infty}\frac{M_t}{t}=0.\ a.s.$$

Lemma 4.2. *Suppose that $(\mu^l)^{1-k}(\mu^u)^k > \frac{(\sigma^l)^{2-2k}(\sigma^u)^{2k}}{2}$. Let $(S(t),I(t),Q(t))$ be a solution of model (4.1) with any initial value $(S(0),I(0),Q(0))\in\Gamma$, then one has*

$$\lim_{t\to\infty}\frac{S(t)}{t}=\lim_{t\to\infty}\frac{I(t)}{t}=\lim_{t\to\infty}\frac{Q(t)}{t}=0,$$

and

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t S(s)dB_1(s)=\lim_{t\to\infty}\frac{1}{t}\int_0^t I(s)dB_2(s)=\lim_{t\to\infty}\frac{1}{t}\int_0^t Q(s)dB_3(s)=0,$$

where

$$(\sigma^l)^{2-2k}(\sigma^u)^{2k}=\max\Big\{(\sigma_1^l)^{2-2k}(\sigma_1^u)^{2k},(\sigma^l)_2^{2-2k}(\sigma_2^u)^{2k},(\sigma^l)_3^{2-2k}(\sigma_3^u)^{2k}\Big\}.$$

Proof. The proof is analogous to [46]. □

Theorem 4.5. *Suppose that* $(\mu^l)^{1-k}(\mu^u)^k > \frac{(\sigma^l)^{2-2k}(\sigma^u)^{2k}}{2}$. *Let* $(S(t), I(t), Q(t))$ *be a solution of the stochastic model (4.1) with initial value* $(S(0), I(0), Q(0)) \in \Gamma$. *Then, when* $R_s < 1$, *the disease of model (4.1) will go to extinction almost surely, i.e*

$$\lim_{t\to\infty} I(t) = 0, \ \ a.s.,$$

and

$$\lim_{t\to\infty} \langle S(t)\rangle = \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}, \ a.s., \ \lim_{t\to\infty}\langle Q(t)\rangle = 0, \ \ a.s.,$$

where

$$R_s = \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{\Big[(\mu^l)^{1-k}(\mu^u)^k+(\alpha_1^l\Lambda^l)^{1-k}(\alpha_1^u\Lambda^u)^k\Big]A_1} - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2A_1} = R_{0b} - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2A_1}. \tag{4.9}$$

A_1 *is given in (1.3).*

Proof. Applying the Itô's formula on $\ln I(t)$, one has

$$\begin{aligned}
\mathrm{d}\ln I(t) =& \left[\frac{\beta(V^*)S(t)}{\Phi} - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} - A_1\right]\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(t)\\
\le& \left[\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k+(\alpha_1^l\Lambda^l)^{1-k}(\alpha_1^u\Lambda^u)^k} - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} - A_1\right]\mathrm{d}t\\
&+ (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(t)\\
=& A_1(R_s-1)\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(t).
\end{aligned} \tag{4.10}$$

Integrating the above inequality (4.10) from 0 to t and then dividing by t on both sides, one gets

$$\frac{\ln I(t)}{t} \le \frac{\ln I(0)}{t} + A_1(R_s-1) + \frac{1}{t}\int_0^t (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(s).$$

By Lemma 4.1 and the strong law of large numbers for martingales [29], one has

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(s) = 0.$$

Then,

$$\limsup_{t\to\infty}\frac{\ln I(t)}{t} \le A_1(R_s-1),$$

when $R_s < 1$, it leads that

$$\lim_{t\to\infty} I(t) = 0. \tag{4.11}$$

Integrating the third equation of the model (4.1) in interval $[0, t]$ and dividing by t, one has

$$\frac{Q(t)-Q(0)}{t} = (\delta^l)^{1-k}(\delta^u)^k\langle I(t)\rangle - A_2\langle Q(t)\rangle + \frac{1}{t}\int_0^t (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q(s)\mathrm{d}B_3(s).$$

Hence,

$$\langle Q(t)\rangle = \frac{1}{A_2}\left[(\delta^l)^{1-k}(\delta^u)^k\langle I(t)\rangle - \frac{Q(t)-Q(0)}{t} + \frac{1}{t}\int_0^t (\sigma_3^l)^{1-k}(\sigma_3^u)^k Q(s)\mathrm{d}B_3(s)\right]. \tag{4.12}$$

From the (4.11) and Lemma 4.2, taking the limit of the equality (4.12), one gets

$$\lim_{t\to\infty}\langle Q(t)\rangle = 0. \ \ a.s. \tag{4.13}$$

Similarly, integrating the first equation of the model (4.1) from 0 to t and dividing by t, one gets

$$\begin{aligned}\frac{S(t)-S(0)}{t} =&(\Lambda^l)^{1-k}(\Lambda^u)^k - (\mu^l)^{1-k}(\mu^u)^k\langle S(t)\rangle + (\gamma^l)^{1-k}(\gamma^u)^k\langle I(t)\rangle \\ &- \beta(V^*)\langle\frac{SI}{\Phi}\rangle + (\varepsilon^l)^{1-k}(\varepsilon^u)^k\langle Q(t)\rangle + \frac{1}{t}\int_0^t(\sigma_1^l)^{1-k}(\sigma_1^u)^k S(s)\mathrm{d}B_1(s).\end{aligned}$$

It follows that

$$\begin{aligned}\langle S(t)\rangle =&\frac{1}{(\mu^l)^{1-k}(\mu^u)^k}\Bigg\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \beta(V^*)\langle\frac{SI}{\Phi}\rangle + (\gamma^l)^{1-k}(\gamma^u)^k\langle I(t)\rangle \\ &+(\varepsilon^l)^{1-k}(\varepsilon^u)^k\langle Q(t)\rangle + \frac{1}{t}\int_0^t(\sigma_1^l)^{1-k}(\sigma_1^u)^k S(s)\mathrm{d}B_1(s) - \frac{S(t)-S(0)}{t}\Bigg\}.\end{aligned} \tag{4.14}$$

According to (4.11), (4.13), Lemma 4.2 and taking the limit of (4.14), one gets

$$\lim_{t\to\infty}\langle S(t)\rangle = \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k}, \quad a.s.$$

□

Remark 4.3. When $(\sigma_2^l)^{1-k}(\sigma_2^u)^k = 0$, R_s degrades to the basic reproduction number R_{0b}. When the parameters of the deterministic model (4.1) are precise, $\alpha_1 = 0$ and $\beta(V^*) = \beta$, the basic reproduction number R_s degrades to the basic reproduction number R_s which has been investigated in [6, 10].

4.5. Persistence in mean of the COVID-19

Lemma 4.3. *[19] Let $f(t) \in C([0,\infty]\times\Omega,(0,\infty))$, if there are two positive constants λ_{00} and λ_{01} such that*

$$\log(f(t)) \geq \lambda_{01}t - \lambda_{00}\int_0^t f(s)ds + F(t), a.s.,$$

for all $t \geq 0$, where $F(t) \in C([0,\infty)\times\Omega,\mathbb{R})$, and $\lim_{t\to\infty}\frac{F(t)}{t} = 0$, a.s. then

$$\lim_{t\to\infty}\inf\frac{1}{t}\int_0^t f(s)ds \geq \frac{\lambda_{01}}{\lambda_{00}}. a.s.$$

Theorem 4.6. *Suppose that* $(\mu^l)^{1-k}(\mu^u)^k > \frac{(\sigma^l)^{2-2k}(\sigma^u)^{2k}}{2}$. *Let* $(S(t), I(t), Q(t))$ *be a solution of the stochastic model (4.1) with initial value* $(S(0), I(0), Q(0)) \in \Gamma$. *Then, when* $R_s > 1$, *the disease will be persistent in mean, i.e.*

$$\begin{aligned}
&\liminf_{t\to\infty}\langle S(t)\rangle \geq \frac{(\Lambda^l\mu^l)^{1-k}(\Lambda^u\mu^u)^k}{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*) + (\mu^l)^{2-2k}(\mu^u)^{2k}},\\
&\liminf_{t\to\infty}\langle I(t)\rangle \geq \frac{A_1(R_s-1)}{m_3}, \ a.s.,\\
&\liminf_{t\to\infty}\langle Q(t)\rangle \geq \frac{(\delta^l)^{1-k}(\delta^u)^k A_1(R_s-1)}{A_2 m_3}, \ a.s.,
\end{aligned}$$

where

$$m_3 = \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta^2(V^*)}{A_3^2} + m_2, \tag{4.15}$$

with

$$m_2 = \left[\frac{(\Lambda^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_2^u)^k\beta(V^*)}{A_3} + \frac{(\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k(\Lambda^l)^{2-2k}(\Lambda^u)^{2k}\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k A_3}\right]. \tag{4.16}$$

A_1, A_2 *are given in (1.3) and*

$$A_3 = (\mu^l)^{1-k}(\mu^u)^k + (\alpha_1^l\Lambda^l)^{1-k}(\alpha_1^u\Lambda^u)^k. \tag{4.17}$$

Proof. Nothing that the function $\frac{\beta(V^*)S}{\Phi}$ can be written as

$$\begin{aligned}
\frac{\beta(V^*)S}{\Phi} =& -\left[\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k} - S\right]\frac{(\mu^l)^{1-k}(\mu^u)^k\beta(V^*)}{A_3\Phi} + \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{A_3}\\
&- \frac{(\Lambda^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_2^u)^k\beta(V^*)I}{A_3\Phi} - \frac{(\Lambda^l\alpha_1^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_1^u\alpha_2^u)^k\beta(V^*)IS}{A_3\Phi}\\
\geq& -\left[\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k} - S\right]\frac{(\mu^l)^{1-k}(\mu^u)^k\beta(V^*)}{A_3} + \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{A_3}\\
&- \left[\frac{(\Lambda^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_2^u)^k\beta(V^*)}{A_3} + \frac{(\Lambda^l\alpha_1^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_1^u\alpha_2^u)^k\beta(V^*)S}{A_3}\right]I\\
\geq& \frac{(\mu^l)^{1-k}(\mu^u)^k\beta(V^*)S}{A_3} - \left[\frac{(\Lambda^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_2^u)^k\beta(V^*)}{A_3}\right.\\
&\left.+\frac{(\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k(\Lambda^l)^{2-2k}(\Lambda^u)^{2k}\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k A_3}\right] I.
\end{aligned}$$

It follows that

$$\begin{aligned}
\mathrm{d}\ln I(t) =& \left[\frac{\beta(V^*)S(t)}{\Phi} - A_1 - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2}\right]\mathrm{d}t + (\sigma_2^l)^{1-k}(\sigma_2^u)^k\mathrm{d}B_2(t)\\
\geq& \left\{\frac{(\mu^l)^{1-k}(\mu^u)^k\beta(V^*)S(t)}{A_3} - \left[\frac{(\alpha_1^l\alpha_2^l)^{1-k}(\alpha_1^u\alpha_2^u)^k(\Lambda^l)^{2-2k}(\Lambda^u)^{2k}\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k A_3}\right.\right.\\
&\left.\left.+\frac{(\Lambda^l\alpha_2^l)^{1-k}(\Lambda^u\alpha_2^u)^k\beta(V^*)}{A_3}\right]I - A_1 - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2}\right\}\mathrm{d}t
\end{aligned}$$

$$+ (\sigma_2^l)^{1-k}(\sigma_2^u)^k \mathrm{d}B_2(t).$$

Integrating the above inequality from 0 to t and then dividing by t on both sides, one gets

$$\begin{aligned}\frac{\ln I(t)}{t} \geq \Bigg\{ & \frac{(\mu^l)^{1-k}(\mu^u)^k \beta(V^*)\langle S(t)\rangle}{A_3} - m_2\langle I(t)\rangle \\ & -A_1 - \frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} + \frac{1}{t}\int_0^t (\sigma_2^l)^{1-k}(\sigma_2^u)^k \mathrm{d}B_2(s)\Bigg\} + \frac{\ln I(0)}{t},\end{aligned}$$

where m_2 are given in (4.16). From (4.14), one has

$$\begin{aligned}\frac{\ln I(t)}{t} \geq \Bigg\{ & \frac{\beta(V^*)}{A_3}\Bigg[(\Lambda^l)^{1-k}(\Lambda^u)^k - \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{A_3}\langle I(t)\rangle \\ & +\frac{1}{t}\int_0^t (\sigma_1)^{1-k}(\sigma_1^u)^k S(s)\mathrm{d}B_1(s) - \frac{S(t)-S(0)}{t}\Bigg] - m_2\langle I(t)\rangle - A_1 \\ & -\frac{(\sigma_2^l)^{2-2k}(\sigma_2^u)^{2k}}{2} + \frac{1}{t}\int_0^t (\sigma_2^l)^{1-k}(\sigma_2)^k \mathrm{d}B_2(s)\Bigg\} + \frac{\ln I(0)}{t}.\end{aligned}$$

It leads to that

$$\frac{\ln I(t)}{t} \geq \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{A_3} - A_1 - \frac{(\sigma_2^l)^{1-k}(\sigma_2^u)^k}{2} - m_3\langle I(t)\rangle + \varphi(t),$$

where

$$\begin{aligned}\varphi(t) = & \frac{\beta(V^*)}{A_3}\left[\frac{1}{t}\int_0^t (\sigma_1^l)^{1-k}(\sigma_1^u)^k S(s)\mathrm{d}B_1(s) - \frac{S(t)-S(0)}{t}\right] \\ & + \frac{1}{t}\int_0^t (\sigma_2^l)^{1-k}(\sigma_2^u)^k \mathrm{d}B_2(s) + \frac{\ln I(0)}{t}.\end{aligned}$$

By the Lemma 4.1 and Lemma 4.2, one has

$$\lim_{t\to\infty}\varphi(t) = 0.$$

Using Lemma 4.3, then

$$\liminf_{t\to\infty}\langle I(t)\rangle \geq \frac{A_1(R_s-1)}{m_3} := I^*, \tag{4.18}$$

where m_3 are given in (4.15). From (4.12) and (4.18), has

$$\begin{aligned}\liminf_{t\to\infty}\langle Q(t)\rangle = & \liminf_{t\to\infty}\Bigg\{\frac{(\delta^l)^{1-k}(\delta^u)^k}{A_2}\langle I(t)\rangle + \frac{1}{A_2 t}\int_0^t (\sigma_3^l)^{1-k}(\sigma_3^u)^k \mathrm{d}B_3(s) \\ & -\frac{Q(t)-Q(0)}{A_2 t}\Bigg\} \\ \geq & \frac{(\delta^l)^{1-k}(\delta^u)^k}{A_2} I^* \\ > & 0.\end{aligned}$$

From the first equation of model (4.1), one has

$$\begin{aligned}\mathrm{d}S(t) \geq& \Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \psi(S,I) - (\mu^l)^{1-k}(\mu^u)^k S\Big\}\mathrm{d}t + (\sigma_1^l)^{1-k}(\sigma_1^u)^k S\mathrm{d}B_1(t)\\ \geq& \left\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \left[\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k} + (\mu^l)^{1-k}(\mu^u)^k\right]S(t)\right\}\mathrm{d}t\\ &+ (\sigma_1^l)^{1-k}(\sigma_1^u)^k S(t)\mathrm{d}B_1(t).\end{aligned}$$

Integrating the above inequality from 0 to t and then dividing by t on both sides, one has

$$\langle S(t)\rangle \geq \frac{\Big\{(\Lambda^l)^{1-k}(\Lambda^u)^k - \frac{S(t)-S(0)}{t} + \frac{1}{t}\int_0^t(\sigma_1^l)^{1-k}(\sigma_1^u)^k S(s)\mathrm{d}B_1(s)\Big\}}{\Big[\frac{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*)}{(\mu^l)^{1-k}(\mu^u)^k} + (\mu^l)^{1-k}(\mu^u)^k\Big]}.$$

It follows that

$$\liminf_{t\to\infty}\langle S(t)\rangle \geq \frac{(\Lambda^l\mu^l)^{1-k}(\Lambda^u\mu^u)^k}{(\Lambda^l)^{1-k}(\Lambda^u)^k\beta(V^*) + (\mu^l)^{2-2k}(\mu^u)^{2k}}.$$

□

Remark 4.4. R_s is actually a stochastic threshold that determines the extinction or persistence in mean of the disease of the stochastic model (4.1). According to the expression of R_s in (4.9), one can see that R_s depends not only on the amount of virus, but also on the intensity of noise. One concludes that larger stochastic noises and small amount of virus are able to suppress the emergence of disease outbreaks.

4.6. Sensitivity factors (SF) of R_s

In order to study the influence of imprecise parameters of the multi-scale model (1.2). In following, one presents some sensitivity factors of interval parameters of R_s. For convenience, one rewrites R_s in the following form:

$$\begin{aligned}R_s =& \frac{\beta(V^*)[\Lambda^l,\Lambda^u]}{\Big([\mu^l,\mu^u] + [\alpha_1^l,\alpha_1^u][\Lambda^l,\Lambda^u]\Big)\Big([\mu^l,\mu^u] + [\omega_2^l,\omega_2^u] + [\delta^l,\delta^u] + [\gamma^l,\gamma^u]\Big)}\\ &- \frac{[\sigma_2^l,\sigma_2^u]^2}{2\Big([\mu^l,\mu^u] + [\omega_2^l,\omega_2^u] + [\delta^l,\delta^u] + [\gamma^l,\gamma^u]\Big)},\end{aligned} \tag{4.19}$$

where

$$\beta(V^*) = \frac{[r^l,r^u]V^*}{[K_w,K_w]V^* + 1},$$

with

$$V^* = \frac{[d_p^l,d_p^u]}{[\beta_w^l,\beta_w^u]}\Big(\frac{([\beta_w^l,\beta_w^u][\pi_\nu^l,\pi_\nu^u]E_p(0)}{[d_{p\nu}^l,d_{p\nu}^u][d_\nu^l,d_\nu^u]} - 1\Big).$$

Firstly, one presents some knowledge about the sensitivity of interval parameters [32]. For a structure which there is n parameters, the parameter vector is denoted by $Z = \{z_1, z_2, \cdots, z_n\}$, where $z_j = [z_j^l, z_j^u]\,(j = 1, 2, \cdots, n)$ [48]. The uncertainty and interval medium-value of z_j are defined by

$$\Delta z_j = (z_j^u - z_j^l)/2, z_j^c = (z_j^l + z_j^u)/2,$$

respectively. Then, the variation coefficient of z_j is defined by $\overline{\delta_j} = \frac{\Delta z_j}{z_j^c}$. To investigate the sensitivity factor, the variation coefficients of all parameters should be same, i.e., $\overline{\delta_i} = \overline{\delta_j}\,(i,j = 1,\cdots,n)$. Suppose there is a decision-making target $[R_s^l, R_s^u]$. Let $[R_{s_j}^l, R_{s_j}^u]$ be the boundary influence value interval of parameters $z_j \in [z_j^l, z_j^u], (j = 1,2,\cdots,n)$ to the decision-making target $[R_s^l, R_s^u]$. When $z_j = [z_j^l, z_j^u]$ is an interval number but the other parameters are assumed to be constant and equal to interval medium-values, the boundary influence value interval $[R_{s_j}^l, R_{s_j}^u]$ can be obtained by interval operation. $[R_{s_j}^l, R_{s_j}^u]$ is a subset of $[R_s^l, R_s^u]$. A sensitivity factor θ_j' is defined by

$$\theta_j' = (R_{s_j}^u - R_{s_j}^l)/(R_s^u - R_s^l),$$

where θ_j' is the sensitivity factor of the parameter $z_j = [z_j^l, z_j^u]$ to the decision-making target $[R_s^l, R_s^u]$. The larger the θ_j', the greater the effect the parameter $z_j = [z_j^l, z_j^u]$ has on the decision-making target $[R_s^l, R_s^u]$. Hence, the sensitivity factors of model parameters are represented by

$$\theta' = \left[\theta_1' \; \theta_2' \cdots \theta_n'\right]. \tag{4.20}$$

Finally, according to the method (4.20), one can obtain the sensitivity factors of $[R_s^l, R_s^u]$ in the following

$$\theta_{R_s}' = \left[\theta_\mu' \; \theta_\Lambda' \; \theta_{\alpha_1}' \; \theta_\gamma' \; \theta_{\omega_2}' \; \theta_\delta' \; \theta_{\sigma_2}' \; \theta_r' \; \theta_{K_w}' \; \theta_{d_p}' \; \theta_{d_\nu}' \; \theta_{d_{p\nu}}' \; \theta_{\beta_w}' \; \theta_{\pi_\nu}'\right],$$

where $\theta_\mu' = (R_{s_\mu}^u - R_{s_\mu}^l)/(R_s^u - R_s^l)$ is the sensitivity factor of parameter $[\mu^l, \mu^u]$ to $[R_s^l, R_s^u]$, $[R_{s_\mu}^l, R_{s_\mu}^u]$ is the boundary influence value interval of the model parameter $[\mu^l, \mu^u]$ to $[R_s^l, R_s^u]$. Similarly, one also can compute the other sensitivity factors, such as θ_Λ', θ_{α_1}', and so on. One can use the sensitivity factors to measure the relative change with respect to the interval parameters of the $[R_s^l, R_s^u]$. The sensitivity factors can provide us some useful strategies to control the COVID-19.

5. Numerical simulations

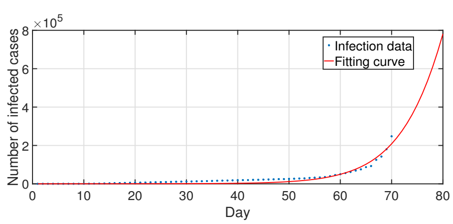
This section gives some numerical simulations to confirm the theoretical results of section 3 and 4 by using real COVID-19 data of Hong Kong from December 21, 2021 to February 28, 2022 [43]. Least Square Method is used to fit the parameters of the deterministic model of the multi-scale model (1.2). For convenience, one supposes $d_p^l = d_p^u$ and considers chest radiograph score [24] as a way to reflect the infected pulmonary epithelial cells of the within-host fast model. The fitting results and parameters are given in Fig 1 (a) and Table 1, respectively. Based on the parameters in Table 1 and (3.3), one has $V^* = 0.01$. It follows from (4.2) one obtains $R_{0b} = 1.91$. One used 70 days of data to predict the results of the next 10 days and found that the fitting results were consistent with the data, as shown in Fig 1 (a).

5.1. The effect of parameter imprecision k and stochastic noise

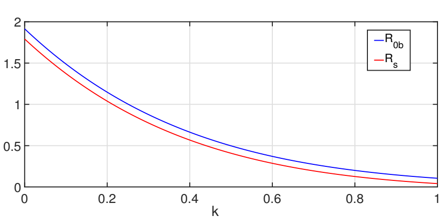
Based on the parameters in Table 1, one plots the variation of R_{0b} and R_s as k varies. From Fig 1 (b), one can see that the basic reproduction number R_{0b} and R_s decrease

Table 1. Parameter descriptions and values of the deterministic model (1.2).

Variables	Description	Initial value	Source
$S(0)$	Susceptible population	7413070	[17]
$I(0)$	Infected population	200	Fitted
$Q(0)$	quarantined population	145	[43]
Parameters	**Description**	**Value**	**Source**
$E_p(0)$	Uninfected epithelial cells without virus	25	[24]
$[\beta_w^l, \beta_w^u]$	The infection rate of virus	[0.44, 0.66]	[24]
$[d_p^l, d_p^u]$	Death rate of uninfected epithelial cells	$[1 \times 10^{-3}, 1 \times 10^{-3}]$	[24]
$[d_{p\nu}^l, d_{p\nu}^u]$	Death rate of infected epithelial cells	[0.088, 0.132]	[24]
$[\pi_\nu^l, \pi_\nu^u]$	Viral production rate	[0.192, 0.288]	[24]
$[d_\nu^l, d_\nu^u]$	Viral elimination rate	[4.288, 6.432]	[24]
$k \in [0, 1]$	Parameter imprecision	0.00113	Fitted
$[\Lambda^l, \Lambda^u]$	Recruitment rate of S	[448, 1246]	Fitted
$[r^l, r^u]$	Transmission rate due to viral load	[0.0409, 0.307]	Fitted
$[K_w^l, K_w^u]$	Half-saturation constant	[63, 604]	Fitted
$[\omega_2^l, \omega_2^u]$	Disease-related death rate in I	$[1.00 \times 10^{-5}, 2.47 \times 10^{-4}]$	Fitted
$[\omega_3^l, \omega_3^u]$	Disease-related death rate in Q	$[2.86 \times 10^{-5}, 1.14 \times 10^{-4}]$	Fitted
$[\alpha_1^l, \alpha_1^u]$	Measure of inhibition effect of S	$[8.28 \times 10^{-4}, 5.60 \times 10^{-3}]$	Fitted
$[\alpha_2^l, \alpha_2^u]$	Measure of inhibition effect of I	$[1.16\times10^{-7}, 8.99\times10^{-5}]$	Fitted
$[\delta^l, \delta^u]$	Rate from I to Q	[0.0758, 0.397]	Fitted
$[\varepsilon^l, \varepsilon^u]$	Recover rate from Q to S	[0.0200, 0.528]	Fitted
$[\mu^l, \mu^u]$	The natural death rate	$[3.77 \times 10^{-5}, 4.56 \times 10^{-5}]$	Fitted
$[\gamma^l, \gamma^u]$	Recover rate from I to S	[0.0867, 0.3]	Fitted
ϵ	Small dimensionless parameter	0.0306	Fitted



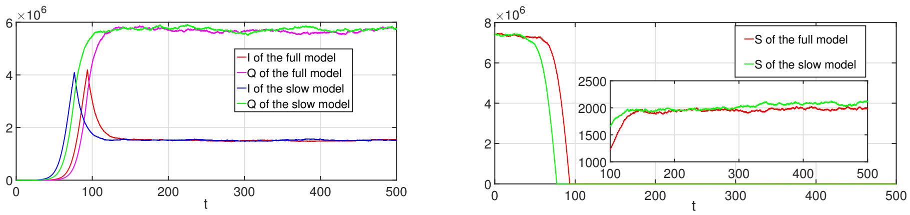
(a)



(b)

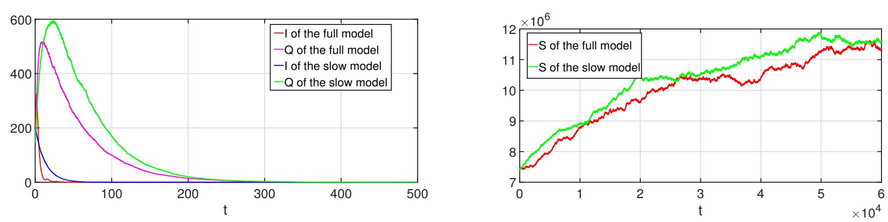
Figure 1. (a) Fitting the deterministic model (1.2) to the real data in Hongkong: the number of COVID-19 infected person; (b) Variation of R_{0b} and R_s as k varies. The parameter values are given in Table 1 and $[\sigma_i^l, \sigma_i^u] = [0.2, 0.3]$, $(i = 1, 2, 3)$.

as the parameter imprecision k increasing. At the same k, R_s is smaller than R_{0b}. This means that stochastic noise can suppress disease spreading. The times series diagrams of the multi-scale stochastic model (1.2) and slow stochastic model (4.1) are obtained by the method in [16]. When $[\sigma_i^l, \sigma_i^u] = [0.003, 0.01]$, $(i = 1, 2, 3)$, from (4.9), one has $(\mu^l)^{1-k}(\mu^u)^k > \frac{(\sigma^l)^{2-2k}(\sigma^u)^{2k}}{2}$, $R_s = 1.9091 > 1$. According to the Theorem 4.6, the disease will persistent in mean, as shown in Fig 2. Similarly, increasing isolation rate to $[\delta^l, \delta^u] = [0.3, 0.4]$ and $[\sigma_i^l, \sigma_i^u] = [0.003, 0.01]$, $(i = 1, 2, 3)$, one gets $R_s = 0.8032 < 1$. According to Theorem 4.5, the disease will go to extinction, as shown in Fig. 3. It implies that increasing isolation rate is a good way to control the disease.



(a) (b)

Figure 2. (a) Times series of $I(t)$ and $Q(t)$ of multi-scale full model (1.2) and slow model (4.1); (b) Times series of $S(t)$ of multi-scale full model (1.2) and slow model (4.1). $[\sigma_i^l, \sigma_i^u] = [0.003, 0.01]$, $(i = 1, 2, 3)$, other parameters are given in Table 1. Initial value $(S(0), I(0), Q(0)) = (7413070, 200, 145)$.



(a) (b)

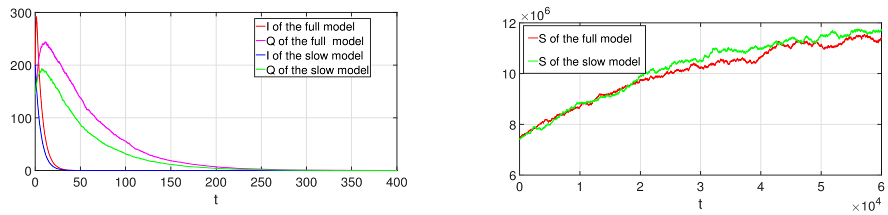
Figure 3. (a) Times series of $I(t)$ and $Q(t)$ of the multi-scale full model (1.2) and slow model (4.1); (b) Times series of $S(t)$ of the multi-scale full model (1.2) and slow model (4.1). $[\delta^l, \delta^u] = [0.3, 0.4]$, $[\sigma_i^l, \sigma_i^u] = [0.003, 0.01]$, $(i = 1, 2, 3)$, other parameters are given in Table 1. Initial value $(S(0), I(0), Q(0)) = (7413070, 200, 145)$.

5.2. The effect of within-host on between-host dynamics

Now, one investigates the potential effect of within-host viral dynamics on the between-host transmission dynamics. Considering the infection rate $[\beta_w^l, \beta_w^u] = [0.01, 0.05]$ of virus, it follows from (3.2) that $R_w = 0.1274 < 1$. According to Theorem 3.1, one has $V^* = 0$. From Fig 4, one can see that

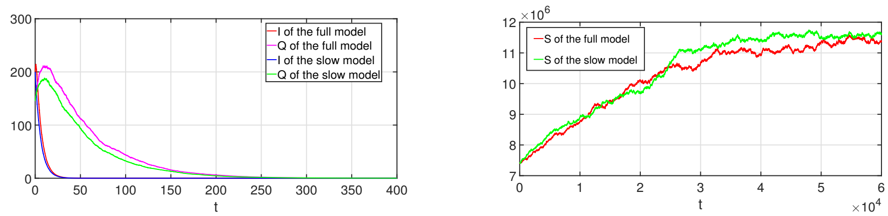
$$\lim_{t\to\infty} I(t) = \lim_{t\to\infty} Q(t) = 0, \ \lim_{t\to\infty} \langle S(t)\rangle = \frac{(\Lambda^l)^{1-k}(\Lambda^u)^k}{(\mu^l)^{1-k}(\mu^u)^k} = 1.189 \times 10^7.$$

Similarly, decreasing the viral production rate to $[\pi_\nu^l, \pi_\nu^u] = [0.0192, 0.0288]$, one obtains $R_w = 0.5597 < 1$. It leads to the disease will go to extinction, as shown in



(a) (b)

Figure 4. (a) Times series of $I(t)$ and $Q(t)$ of the multi-scale full model (1.2) and slow model (4.1); (b) Times series of $S(t)$ of the multi-scale full model (1.2) and slow model (4.1). $[\beta_w^l, \beta_w^u] = [0.01, 0.05]$, other parameter values are given in Table 1. Initial value $(S(0), I(0), Q(0)) = (7413070, 200, 145)$.



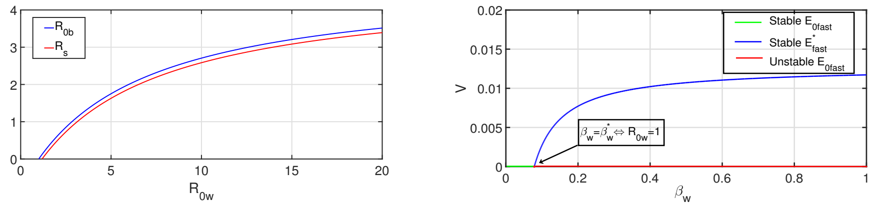
(a) (b)

Figure 5. (a) Times series of $I(t)$ and $Q(t)$ of the multi-scale full model (1.2) and slow model (4.1). (b) Times series of $S(t)$ of the multi-scale full model (1.2) and slow model (4.1). $[\pi_\nu^l, \pi_\nu^u] = [0.0192, 0.0288]$, other parameter values are given in Table 1. Initial value $(S(0), I(0), Q(0)) = (7413070, 200, 145)$.

Fig 5. This suggests that improving the viral clearance rate and inhibiting the viral replication rate is a good way to control the disease. Therefore, it is very important to eliminate the virus at the lowest level on within-host scale. Further, one plots the variation of R_{0b} and R_s as R_{0w} varies. Clearly, R_{0b} and R_s is increasing as R_w increasing, as shown in Fig 6 (a). Moreover, from (3.4), one obtains $\beta_w^* = 0.0786$. According to Theorem 3.3, the uninfected equilibrium E_{0fast} of fast model (3.1) changes its stability from stable to unstable and a globally asymptotically infected equilibrium appears when β_w from $\beta_w < \beta_w^* = 0.0786 \Leftrightarrow R_{0w} < 1$ to $\beta_w > \beta_w^* \Leftrightarrow R_{0w} > 1$, as shown in Fig 6 (b). It implies that fast model (3.1) undergoes forward bifurcation at $\beta_w = \beta_w^* \Leftrightarrow R_{0w} = 1$. Meanwhile, from Fig. 2 to Fig. 5, one can see that the dynamics of the stochastic multi-scale model (1.2) is consistent with the slow stochastic model (4.1). It is helpful for us to use slow stochastic model (4.1) to approximate to investigate the stochastic multi-scale model (1.2).

5.3. Sensitivity factors (SF) of R_s

Next, one gives some sensitivity analysis of R_s. For convenience and precision, based on the same variation coefficient $\overline{\delta} = 0.1$, one assumes parameters in Table 2. By the method of section 4 and the arithmetic operations of interval numbers in definition 2.1, the sensitivity factors of R_s can be calculated and given in Table 2. From the Table 2, one can see the most sensitive parameter of R_s is $[\beta_w^l, \beta_w^u]$. Meanwhile, $[\Lambda^l, \Lambda^u]$, $[\pi_\nu^l, \pi_\nu^u]$ and $[d_p^l, d_p^u]$ have an important effect on R_s. The sensitivity factors are useful for us to make some control strategies. For instance, reducing the recruitment rate of susceptible population, reducing viral production



(a) (b)

Figure 6. (a) Variation of R_{0b} and R_s as R_{0w} varies. $[\sigma_i^l, \sigma_i^u] = [0.2, 0.3]$, $(i = 1, 2, 3)$, other parameters are given in Table 1. (b) Forward bifurcation diagram of fast model (3.1) with parameters in Table 1.

rate, social distancing, wearing masks, and so on.

Table 2. Parameter values and sensitivity factors (SF) of R_s

Parameter	$[\Lambda^l, \Lambda^u]$	$[\mu^l, \mu^u]$	$[\alpha_1^l, \alpha_1^u]$	$[\gamma^l, \gamma^u]$	$[\omega_2^l, \omega_2^u]$	$[\delta^l, \delta^u]$	$[\sigma_2^l, \sigma_2^u]$
Values	$[500, \frac{5500}{9}]$	$[\frac{4}{10^5}, \frac{44}{9\times10^5}]$	$[\frac{1}{10^3}, \frac{11}{9\times10^3}]$	$[\frac{1}{10}, \frac{11}{90}]$	$[\frac{5}{10^5}, \frac{55}{9\times10^5}]$	$[\frac{1}{5}, \frac{11}{45}]$	$[\frac{8}{10^2}, \frac{88}{9\times10^2}]$
SF	0.1195	1.234×10^{-5}	0.0598	0.0199	1×10^{-5}	0.0400	0.0011
Parameter	$[r^l, r^u]$	$[K_w^l, K_w^u]$	$[d_p^l, d_p^u]$	$[d_\nu^l, d_\nu^u]$	$[d_{p\nu}^l, d_{p\nu}^u]$	$[\beta_w^l, \beta_w^u]$	$[\pi_\nu^l, \pi_\nu^u]$
Values	$[\frac{1}{10}, \frac{11}{90}]$	$[100, \frac{1100}{9}]$	$[\frac{1}{10^3}, \frac{11}{9\times10^3}]$	$[5, \frac{55}{9}]$	$[\frac{1}{10}, \frac{11}{90}]$	$[\frac{1}{2}, \frac{55}{90}]$	$[\frac{1}{5}, \frac{22}{90}]$
SF	0.0592	0.0279	0.0872	0.0533	0.0533	0.1418	0.1091

6. Conclusions and suggestions

In order to explore the potential effect of within-host viral dynamics on the between-host transmission dynamics under environmental noises. This paper uses interval-valued functions to investigate the dynamics of a stochastic multi-scale COVID-19 model (1.2) that coupling within-host viral and between-host transmission dynamics. The model is composed of the within-host fast time model and the between-host slow time stochastic model. One obtains some results which can provide us some helpful measures to control the COVID-19 in the uncertain stochastic environment. More precisely, these results can be concluded as follows:

(i) The dynamics of the fast model (3.1) can be governed by the basic reproduction number R_{0w}. When $R_{0w} < 1$, uninfected equilibrium E_{0w} is globally asymptotically stable. When $R_{0w} > 1$, infected equilibrium E^*_{fast} is globally asymptotically stable. The model (3.1) undergoes forward bifurcation at $R_{0w} = 1$.

(ii) The dynamics of the coupling slow stochastic model (4.1) can be governed by the stochastic threshold R_s. When $R_s < 1$, the disease will go to extinction. When $R_s > 1$, the disease will persistent in mean. One finds that R_s is an increasing function of R_{0w}.

(iii) Numerical analysis reveals that the dynamics of the stochastic model (4.1) are similar to the multi-scale stochastic model (1.2), it provides us a simple method to investigate the multi-scale model (1.2). When $R_{0w} < 1$ or ($R_{0w} > 1$

and $R_s < 1$), the disease will go to extinction of the multi-scale model (1.2). When $R_{0w} > 1$ and $R_s > 1$, the disease will persistent in mean of the multi-scale model (1.2).

(iv) Some numerical simulations are presented to demonstrate the results. One finds that large noise intensity $[\sigma_2^l, \sigma_2^u]$, quarantine rate $[\delta^l, \delta^u]$, inhibition effect $[\alpha_1^l, \alpha_1^u]$ of S, parameter imprecision k, small viral infection rate $[\beta_w^l, \beta_w^u]$ and viral production rate $[\pi_\nu^l, \pi_\nu^u]$ can suppress the breakout of COVID-19.

Based on the obtained results, one presents some suggestions which can effectively control the COVID-19 in the world. The suggestions are given in the following:

(i) Improve the true accuracy of epidemic data. The more realistic the data, the better the control of the disease.

(ii) When the COVID-19 epidemic occurs, the quarantine of infected individual should be used immediately. It's worth saying that the quarantine policy is very useful for the mutating COVID-19, such as Delta, Omicron and so on.

(iii) Medical scientist should speed up the research on miracle drugs to suppress the virus's replication and promote viral clearance.

(iv) Some protective measures, such as wearing masks, speeding up the disease detection, avoiding crowds should be continued and encouraged in society. At the same time, it is also necessary to exercise regularly to improve immunity.

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Competing interests

The authors declare that they have no competing interests.

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