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Asymptotic mean-square stability analysis and simulations of a stochastic model for the human immune response with memory

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ASYMPTOTIC MEAN-SQUARE STABILITY ANALYSIS AND SIMULATIONS OF A STOCHASTIC MODEL FOR THE HUMAN IMMUNE RESPONSE WITH MEMORY

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Abstract

In this thesis we extend a deterministic model for the Human Immune response, consisting of a non-linear system of differential equations with distributed time delay, which was introduced by Beretta, Kirshner and Marino in 2007, by incorporating stochastic perturbations with multiplicative noise around the equilibria of the deterministic model. Our aim is to study the robustness of the equilibria of the deterministic model for the human immune response system with respect to fluctuations due to considering the human body as a noisy environment. We do this by analysing the asymptotic mean-square stability of the equilibria of our stochastic model. Our work could be divided roughly into two parts. In the first part we analyse the stability of a general nonlinear system of stochastic differential equations with distributed memory terms by studying the stability properties of the linearisation in the first approximation. First of all we state, using Halanay's inequalities, comparison results useful in the investigation of exponential mean square stability of linear stochastic delay differential systems with distributed memory terms. Then we provide conditions under which the asymptotic mean square stability of a nonlinear system of stochastic delay differential equations is implied by the exponential mean square stability of the linearised stochastic delay system in the first approximation. In the second part we apply the theoretical results obtained in the first part to investigate the stochastic stability properties of the equilibria of our stochastic model of human immune response. The theoretical results are illustrated by numerical simulations and an uncertainty and sensitivity analysis of our stochastic model, suggesting that the deterministic model is robust with respect to the stochastic perturbations.

Sommario

In questa tesi viene esteso un modello deterministico per la risposta immunitaria umana, consistente in un sistema non lineare di equazioni differenziali con ritardo distribuito, che è stato introdotto da Beretta, Kirshner e Marino nel 2007, mediante perturbazioni stocastiche con rumore moltiplicativo intorno ai punti di equilibrio del modello deterministico. L'obiettivo è studiare la robustezza dei punti di equilibrio del modello deterministico per la risposta immunitaria umana rispetto alle fluttuazioni dovute al considerare il corpo umano come un ambiente rumoroso. A questo scopo è stata analizzata la stabilità asintotica media quadratica degli equilibri del nostro modello stocastico. Questo lavoro è diviso in due parti. Nella prima parte si analizza la stabilità di un sistema generale non lineare di equazioni differenziali stocastiche con ritardo distribuito, studiando le proprietà di stabilità della linearizzazione in prima approssimazione. Prima sono stati ottenuti, usando le disuguaglianze di Halanay, teoremi del confronto utili per l'analisi della stabilità esponenziale media quadratica dei sistemi lineari stocastici con memoria distribuita. In seguito sono state trovate le condizioni per le quali la asintotica stabilità media quadratica di un sistema non lineare di equazioni differenziali stocastiche con ritardo è dovuta alla stabilità esponenziale media quadratica del sistema stocastico linearizzato in prima approssimazione. Nella seconda parte vengono applicati i risultati teorici ottenuti nella prima parte per indagare le proprietà di stabilità stocastica dei punti di equilibrio del nostro modello stocastico di risposta immunitaria umana. I risultati teorici sono illustrati da simulazioni numeriche e da un'analisi di incertezza e sensibilità del nostro modello stocastico, suggerendo che il modello deterministico è robusto rispetto alle perturbazioni stocastiche.

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1

Introduction

Numerous problems in many areas of science and technology are modelled by using deterministic differential equations. However, during the observation of reality we often deal with phenomena which, under the same conditions, do not behave as predicted by the deterministic model. Such phenomena are subject to some unpredictable effects such as random variations. Thus, if we want to obtain a more realistic formulation for the differential equations arising in applied sciences we need to take into account uncertainties and random noise associated with the processes considered above. By incorporating random elements (random fluctuations such as white noise or jump processes) in a differential equation system, a system of stochastic differential equations arises. Stochastic models have been used with great success in a variety of application areas, including biology, epidemiology, mechanics, economics and finance. Unlike the deterministic model, the stochastic models provide only the probability of an outcome, since the solution of the stochastic differential equations is a stochastic process. It is possible to study the behaviour of this process by studying the entire probability distribution over time, or, when this is not possible, by obtaining the moments of the distribution, such as mean and variance. Stochastic models can arise if we assume that a physical system operates in a noisy environment. It happens, for example, with biological or ecological systems in which the interaction of the components with the environment is noisy. In this case, by the introduction of noise representing the environmental fluctuations, the deterministic differential equations modelling the processes are called stochastic differential equations. If we consider the external noise arising from random fluctuations of some parameters involved in the model around some given

values, then we say that the stochastic system obtained has multiplicative noise. Instead, if the fluctuations considered influence the system from the outside, i.e. when the noise term does not depend on the state variable, then we are dealing with additive noise systems. Interesting reviews of stochastic modelling and applications of stochastic processes in biology can be found in [1, 2]. When evolution of a system depends of the past history of the state, we are led to a system of delay differential equations. Discrete and continuous delays have been considered and incorporated into many biological models, obtaining descriptions of more realistic situations. We can mention for example the introduction of delay terms modelling the incubation time into the model for marine bacteriophage infection by Beretta and Kuang [3] or the introduction of intracellular delay from drug perturbation experiments into models of virus infection [4]. Stochastic delay differential equations, which generalize both deterministic delay differential equations and stochastic differential equations, give us an additional degree of realism. They are attracting an increasing interest in biomathematical modelling not only because they give us a mathematical formulation of more realistic situations, but also because it is possible to analyse the robustness of the positive equilibria of the deterministic model with respect to the fluctuations of the environment. In other words it is possible to study the effects of environmental noise on the stability properties of equilibria of the original deterministic model. To this aim in 1998 Beretta, Kolmanovskii and Shaikhet introduced a noise formulation considering stochastic perturbations of white noise type, directly proportional to distances of variables from values of the equilibrium point of an epidemic model with time delays [5]. In 2002 Carletti used this method to investigate the robustness of stability of an equilibrium point of a stochastic model for phage-bacteria interaction in an open marine environment [6]. Then it was applied by other authors for different models in biology, ecology and medicine (*e.g.*, [7, 8]).

When a deterministic model is perturbed by noise within this framework, it is possible to study the stochastic stability of the equilibrium point and then compare them with the properties of the same equilibrium in the deterministic case. But there is a question to ask: *what is the stochastic stability*? In general the concept of stability of an equilibrium of a differential equation concerns the property to change slightly under slight perturbations in the initial data and the theory of stability of deterministic systems is well developed, since 1892 with Lyapunov's work.

The stochastic stability theory is quite recent. It was initialised in 1960 by Kac and Krasovskii [9] and then developed by Hasminskii in [10] with the construction of *stochastic Lyapunov functions*. They considered, essentially, instead of the derivative of Lyapunov functions along the sample path, the expectation of this derivative. In 1995 the general Lyapunov's method was proposed by Kolmanovskii and Shaikhet for stochastic differential equations with time-lag and developed later consistently for stochastic difference equations with discrete time and continuous time [11, 12]. In 1996 Mao, developing a method used by Razumikhin in [13, 14] for the ordinary differential equations, obtained theorems on exponential p-stability for stochastic delay differential equations [15]. Unfortunately every construction of Lyapunov functionals is always related to the form of the equation under stability analysis, which means that it can be difficult when the stochastic delay differential equations are quite complicated (i.e. nonlinear systems, several parameters involved, order bigger than one, etc.). For nonlinear equations, stability of equilibrium solutions (either trivial or not) can be investigated by the method of *stability in the first approximation*, i.e to reduce the study of stability to the linearised versions around the equilibrium point, obtained from the original systems by dropping terms of higher than first order. Stability results in this direction for stochastic delay differential equations are not so developed. In [16] we can find some results for stability in the first approximation for nonlinear stochastic delay differential equations where the linearised equations are no longer stochastic, but deterministic. With our work we fill this *gap* in the stochastic stability theory by construction of stability theorems concerning the mean square stability, via a combination of comparison and Lyapunov function techniques, either regaining or extending Mao's results. In the literature a similar result was obtained in [17], but with different methods.

In this thesis we are interested in studying the robustness of the equilibria of the deterministic model of the human immune response system with respect to fluctuations due to considering the human body as a noisy environment. We perturb the deterministic model introduced in 2007 by Beretta, Kirshner and Marino [18] by using the noise formulation described above. The stochastic model we obtained, which describes a more realistic situation than the deterministic counterpart, consists of a nonlinear system of five stochastic differential equations with distributed delays and with 12 parameters involved. This means that the stochastic system is quite complicated and it

is reasonable to look for the stability in the first approximation theory to apply to this case.

Our work could be divided roughly into two parts.
In the first part we analyse the stability of a general nonlinear system of stochastic differential equations with the distributed memory terms by studying the stability properties of the linearisation in the first approximation. First of all we state, using Halanay's inequalities, comparison results useful in the investigation of exponential mean square stability of linear stochastic delay differential systems with distributed memory terms. Then we provide conditions under which the asymptotic mean square stability of a nonlinear system of stochastic delay differential equations is implied by the exponential mean square stability of the linearised stochastic delay system in the first approximation.

In the second part we apply the theoretical results obtained in the first part to investigate the stochastic stability properties of the equilibria of our stochastic model of human immune response. We also perform some numerical simulations to illustrate the results obtained. We want to point out that in the deterministic analysis of the model for the human immune response considered there exists an analytical investigation of stability properties only for the boundary equilibrium but not for the positive one. However, in the literature it is possible to find some information about the existence of stability switches for the positive equilibrium by a sensitivity analysis of the deterministic model [18]. Since we are interested in comparing the deterministic stability properties of equilibria with their stochastic counterparts, we conduct in the last chapter of this thesis an uncertainty and sensitivity analysis of our stochastic model and then compare our results with the deterministic information.

In detail this thesis is organized as follows.

In Chapter 2 we give an introduction to the theory of stochastic differential equations, with and without delay. We pay particular attention to the Itô stochastic calculus and the theorems of existence and uniqueness of solution.
In Chapter 3 we introduce the most commonly used definitions of stochastic stability. Then we provide an overview of stochastic stability theory. In the last part of this chapter we depict the problem of constructing a suitable stability theory in the first approximation for stochastic delay differential equations.

In Chapter 4 with the first two sections we focus our attention on the proofs of comparison theorems. We obtain conditions to guarantee the asymptotic mean square stability for the equilibrium of stochastic differential equations with distributed memory terms using a generalisation of the Halanay inequality. In the third and last section of this chapter we construct stability theorems which allow us to create the basis of an original first approximation theory for stochastic delay differential equations not previously existent.
In Chapter 5 we formulate a new stochastic model for the human immune response. We perturb the deterministic system introduced by [18] by multiplicative noise, considering stochastic perturbations of white noise type, directly proportional to distances of variables from values of the boundary equilibrium point. We apply the stability theorems obtained in Chapter 4 to study the stochastic stability properties of equilibria of the stochastic immune model. We obtain conditions of stability in terms of thresholds of the parameter values and the amplitude of noise.
In Chapter 6 we start giving a brief overview of numerical methods for stochastic differential equations (with and without delay). Our aim in this chapter is to perform simulations of the stochastic model of human immune response to illustrate the sufficient conditions on the parameters obtained in Chapter 5 which guarantee asymptotic mean-square stability of equilibrium point. A biological discussion of information obtained is also provided.
Finally in Chapter 7 we implement Matlab codes to perform the uncertainty and sensitivity analysis of the stochastic immune model. We investigate the uncertainty in the model output generated from uncertainty in parameter inputs. We also obtain a classification of suitable thresholds of the delays to predict the stability switch of the positive equilibrium point of our stochastic immune model. We conclude with a discussion of biological implications of these results to carrying out research on the human immune response.

The contributions contained in the chapters 4, 5, 6, 7 are parts of works currently in preparation.

2

Background to stochastic differential equations: SODEs and SDDEs

The aim of this chapter is to give an introduction to the theory of stochastic differential equations, with and without delay, paying particular attention to the Itô stochastic calculus and the theorems of existence and uniqueness of solution. Only a brief overview about the main contents is given. For a deeper treatments of the topics we refer to the bibliography.

2.1 Stochastic ordinary differential equations (SODEs)

Differential equations play a central role in applications of mathematics to natural sciences. However, real processes always contain some elements characterising physical features of the phenomenon and environment which are experimentally determined. Due to errors in the measurement and inherent randomness of a phenomenon many real processes modelled by deterministic systems do not behave as predicted. A similar situation occurs when we think about initial conditions. In theory they are assumed to be given. In reality, however, these conditions are known only within certain ranges of values and it seems reasonable to treat the data as random. Hence a more realistic formulation of the differential equation models arising in applied sciences should include random effects disturbing the system. There exist several ways to introduce

randomness in a differential equation. For example it is possible to randomise the initial conditions. Such an equation is called a *random differential equation* and the solutions are differentiable functions. Another way to randomize a differential equations could be the following. Consider a deterministic differential equation

$$\frac{dX(t)}{dt} = h(t, X(t)).$$

If h is subject to some random environmental noise we can consider

$$h = f + g \cdot \text{“noise”}$$

and then

$$\frac{dX(t)}{dt} = f(t, X(t)) + g(t, X(t)) \cdot \text{“noise”}.$$

It is reasonable to look at some stochastic process $\xi(t)$ representing the “noise” . In stochastic theory $\xi(t)$ is called a *white noise*. It does not exist in the conventional sense, but it is a useful mathematical idealisation for describing random fluctuations which are practically uncorrelated for different instants of time.

Differential equations where the randomness is introduced in this way, *i.e.*, via an additional random noise term, are called *stochastic ordinary differential equations* (SODEs) and the solutions have non differentiable sample paths.There are other ways to introduce noise and obtain SODEs, *e.g.*, SODEs arise as a limit of discrete stochastic system in population dynamics, chemical kinetics or finance. Accordingly, any solution of SODEs will involve some randomness and we can only find its probabilistic properties. In order to give a mathematical definition of the SODEs, we are going to introduce in the next sections the concepts of the stochastic process and stochastic integral. There are several books dedicated to the study of stochastic calculus and SODEs (see [19, 20, 21, 22]). We mainly refer to the books by Mao [23], Øksendal [24], Mikosch [25] and Allen [1]. For an introduction to the study of stochastic differential equations we refer to [26].

2.1.1 Stochastic Processes

Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a probability space. We define as a *stochastic process* a family of $\mathbb{R}^d$-valued random variables $\{X(t)\}_{t \in I}$, where the parameter set I could be finite or infinite. It is possible to regard a stochastic process as a function of two variables

$X : I \times \Omega \to \mathbb{R}^d$. For a fixed $t \in I$, $X(t) : \Omega \to \mathbb{R}^d$ is an $\mathbb{R}^d$-valued random variable and for a fixed $\omega \in \Omega$, $X(.,\omega) : I \to \mathbb{R}^d$ is a function of time named the *sample path* or *trajectory*. From now on we use the notation $X(t)$ to refer to a stochastic process, with the implicit dependence on $\omega \in \Omega$. Let $\{\mathcal{F}_t\}_{t\geq 0}$ be a filtration of $\mathcal{F}$, *i.e.*, a family of increasing sub-σ-algebras of $\mathcal{F}$. A stochastic process $X(t)$ is then said to be *adapted* to the filtration $\{\mathcal{F}_t\}_{t\geq 0}$ if for every $t \geq 0$, $X(t)$ is $\{\mathcal{F}_t\}$-measurable.
Two important classes of stochastic processes are martingales and Markov processes. An $\mathbb{R}^d$-valued $\{\mathcal{F}_t\}$-adapted integrable process $X(t)$ is called a *martingale* with respect to the filtration $\mathcal{F}_t$, if $\mathbb{E}(X(t)|\mathcal{F}_s) = X(s)$ almost surely for all $0 \leq s < t < \infty$. Then a martingale is a " fair game " , where for X the best prediction of the future value $X(t)$, given $\mathcal{F}_s$, is the present value $X(s)$. It is clear that this is going to change if we consider another filtration. This means it is necessary to say which filtration is considered. An $\mathbb{R}^d$-valued $\{\mathcal{F}_t\}$-adapted process $X(t)$ is called a *Markov process* if it satisfies the Markov property, *i.e.*, for all $0 \leq s < t < \infty$ and $B \in \mathcal{B}$, the Borel σ-algebra of $\mathbb{R}^d$, $\mathbb{P}(X(t) \in B|\mathcal{F}_s) = \mathbb{P}(X(s) \in B|X(s))$. The Markov property means that, given a Markov process, the past and the future are independent when the present is known, in other words it is a no-memory process. Let $\mathbb{P}(x, s; B, t)$ be the transition probability of the Markov process $X(t)$, *i.e.*, the function defined on $0 \leq s \leq t < \infty$, $x \in \mathbb{R}$ and $B \in \mathcal{B}$, which gives the probability of a transition from a state x at time s to a state B belonging to a Borel set at time t. In terms of the transition probability, the Markov property becomes $\mathbb{P}(X(t) \in B|\mathcal{F}_s) = \mathbb{P}(X(s), s; B, t)$. Considering the transition probability density function $p(x, s; t, y) = \frac{\partial}{\partial y}\mathbb{P}(X(t), y|X(s) = x)$, we can give the following definition.

Definition 2.1.1. *Let $X(t)$ be a Markov process with $p(x, s; t, y)$ transition probability density function (p.d.f.). Then $X(t)$ is a* diffusion process *if its p.d.f. satisfies the following three properties for any $\varepsilon > 0$ and $x \in (-\infty, \infty)$*

1. $\lim_{\Delta t\to 0} \frac{1}{\Delta t} \int_{|y-x|>\varepsilon} p(x, s; y, s + \Delta t) = 0$
2. $\lim_{\Delta t\to 0} \int_{|y-x|\leq\varepsilon} (y - x)p(x, s; y, s + \Delta t) = f(x, s)$
3. $\lim_{\Delta t\to 0} \int_{|y-x|\leq\varepsilon} (y - x)^2 p(x, s; y, s + \Delta t) = g(x, s)$.

where the functions $f(x, s)$ and $g(x, s)$ are called the drift and the diffusion.

The first condition states that the probability of a transition over a small time interval is negligible. The second and the third conditions are restrictions of the infinitesimal mean and variance. It is possible to show that these three conditions follow from stronger conditions [1], which can be expressed in terms of the expectation as follows

1'. $\lim_{\Delta t\to 0} \frac{1}{\Delta t}\mathbb{E}(|\Delta(X(s))|^{\delta}|X(s)=x)=0 \qquad \delta>2$

2'. $\lim_{\Delta t\to 0} \mathbb{E}(|\Delta(X(s))||X(s)=x)=f(x,s)$

3'. $\lim_{\Delta t\to 0} \mathbb{E}(|\Delta(X(s))|^{2}|X(s)=x)=g(x,s).$

where $\Delta X(s)=X(s+\Delta t)-X(s)$.

Markov processes and martingales are different classes of stochastic process, but they can coincide. The most important example of a diffusion process and a martingale is the Wiener process, *i.e.*, the stochastic process used to describe Brownian motion mathematically. In 1827 Robert Brown, an Scottish botanist studying pollen particles floating in water under the microscope, noticed that the pollen grains jiggle about. In 1905 Albert Einstein realized that the jiggling of the pollen grains seen in Brownian motion was due to molecules of water hitting the tiny pollen grains and received the Nobel prize for his work. In 1923 Norbert Wiener laid the mathematical foundation for Brownian motion by a continuous-time stochastic process.

Definition 2.1.2. *Let $(\Omega,\mathcal{F},\mathbb{P})$ be a probability space with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$. A* Wiener process *is a real-valued continuous $\{\mathcal{F}_t\}$-adapted process $W(t)$ with the following properties*

1. $\mathbb{P}(W(0)=0)=1 \quad a.s.$
2. *For $0\leq s<t<\infty$, the increment $W(t)-W(s)$ is normally distributed with mean zero and variance $t-s$.*
3. *For $0\leq s<t<\infty$ the increment $W(t)-W(s)$ is independent of $\mathcal{F}_s$.*

The filtration $\{\mathcal{F}_t\}$ is part of the definition of a Wiener process, but it is possible to speak of a Wiener process on a probability space $(\Omega,\mathcal{F},\mathbb{P})$ without filtration when the *natural filtration* is used. In this case the third property is replaced by

3.' For $0 < t_0 < t_1 < \cdots < t_k < \infty$, the increments $W(t_i) - W(t_{i-1})$ and $W(t_k) - W(t_{k-1})$, with $1 \leq i, k$, $i = k$ are independent.

From Definition 2.1.2 it is easy to deduce that the Wiener process has the following properties

(a) $W(0) = 0 \quad a.s.$

(b) $\mathbb{E}(W(t)) = 0.$

(c) $\mathrm{Var}[W(t) - W(s)] = t - s$ for all $0 \leq s < t.$

The p.d.f. of a Wiener process is

$$p(x, s; y, t) = \frac{1}{\sqrt{2\pi t}} \exp\left(\frac{-(y-x)2}{2t}\right),$$

which satisfies the three conditions of Definition 2.1.1 and also the three stronger conditions, with $\delta = 4$. Hence we have

$$\mathbb{E}(\Delta W(t)) = 0 \qquad \mathbb{E}([\Delta W(t)]^2) = \Delta t \qquad \mathbb{E}([\Delta W(t)]^4) = 3(\Delta t)^2.$$

It follows that the Wiener process is a martingale and a diffusion process.

It is necessary to give a new definition of a stochastic integral.

2.1.2 Stochastic integral and Itô 's formula

The classical integrals fail when the integrand or the integrator are Wiener sample paths. A real-valued function f on $[0, 1]$ is said to have bounded p-variation for some $p > 0$ if $sup_\tau \sum_{i=1}^{n} |h(t_i) - h(t_{i-1})|^p < \infty$ when the supremum is taken over all partitions τ of $[0, 1]$. Suppose that f and g are two $\mathbb{R}^d$-valued functions on $[0, 1]$. It easy to prove that sufficient conditions for the existence of the Riemann-Stieltjes integral $\int_0^1 f(t)dg(t)$ are that f and g do not have discontinuities at the same point $t \in [0, 1]$, f has bounded p-variation and g has bounded q-variation for some $p, q > 0$ such that $p^{-1} + q^{-1} > 1$ [27].

Let $W(t)$ be a Wiener process. We know from Definition 2.1.2 that on fixed intervals, sample paths of $W(t)$ have bounded p-variation for $p > 2$ and unbounded p-variation

for $p \leq 2$. Since it is known that if a function f has bounded variation, then f has bounded variation, we have the following condition of existence.

Let f be a deterministic function or the sample path of a stochastic process. If f is differentiable with a bounded derivative on $[0, 1]$, then the Riemann-Stieltjes integral

$$\int_0^1 f(t)dW(t)$$

exists for every Wiener sample path $W(t)$.
This condition is satisfied for several functions (*e.g.*, e^t, $sin(t)$, t^p for $p \geq 0$), but it is not satisfied for the Riemann-Stieltjes integral $\int_0^t g(s)dW(s)$, where g is a stochastic process. We are going to define the stochastic integral of a stochastic process g by an approximation procedure of *simple processes*, *i.e.*, simple random step functions.
Let $\mathcal{L}^2(\mathbb{R}_+)$ be the space of all real valued measurable $\mathcal{F}_t$-adapted stochastic processes g such that

$$\mathbb{E}\left(\int_0^t g^2 ds\right) < \infty.$$

and consider the partition $\tau_n : 0 = t_0 < t_1 < \cdots < t_n = t$

Lemma 2.1.3. *If $g \in \mathcal{L}(\mathbb{R}_+)$ there exists a sequence of bounded step processes $g^n \in \mathcal{L}(\mathbb{R}_+)$ such that*

$$\mathbb{E}\left(\int_0^t |g(s) - g^n(s)|^2 ds\right) \to 0.$$

Definition 2.1.4. *If $g \in \mathcal{L}(\mathbb{R}_+)$ and g^n is the step process given by Lemma 2.1.3. Then there exists the limit*

$$\int_0^t g(s)dW(s) := \lim_{n\to\infty} \int_0^t g^n(s)dW(s). \tag{2.1}$$

This limit is called the Itô integral.

Given the definition of the Itô integral, the classical chain rule of integration is not satisfied (for details we refer to [25]). It becomes necessary, then, to find a chain rule which is well suited for Itô integration and *Itô 's formula* it is what we need. The Itô formula (or *Itô lemma*) is not only useful for evaluating Itô integrals, but is also a very important tool for stochastic analysis. The Itô formula can be considered the stochastic analogue of the classical chain rule of differentiation.
Before we introduce this formula, we need the following definition. Let $\mathcal{L}^1(\mathbb{R}_+;\mathbb{R})$and $\mathcal{L}^2(\mathbb{R}_+;\mathbb{R})$ be the spaces of all real-valued measurable functions f such that $\int |f(s)|ds < \infty$ and $\left(\int |f(s)|^2 ds\right)^{\frac{1}{2}} < \infty$, respectively.

Definition 2.1.5. *Let $W(t)$ be a one-dimensional Wiener process on the probability space $(\Omega, \mathcal{F}_t, \mathbb{P})$. A continuous adapted process $X(t)$ is defined to be an* Itô process *if it is of the form*

$$X(t) = X(0) + \int_0^t f(s)ds + \int_0^t g(s)dW(s) \tag{2.2}$$

where $f \in \mathcal{L}^1(\mathbb{R}_+; \mathbb{R})$ and $g \in \mathcal{L}^2(\mathbb{R}_+; \mathbb{R})$.

The first integral is a Riemann integral and the second integral is an Itô integral. It is often used to define that $X(t)$ has stochastic differential $dX(t)$ on $t \geq 0$ given by

$$dX(t) = f(t)dt + g(t)dW(t). \tag{2.3}$$

Let $C^{2,1}(\mathbb{R}^d \times \mathbb{R}_+; \mathbb{R})$ denote the family of all real-valued functions $V(x,t)$ that are continuously twice differentiable in X and once in t. If $V \in C^{2,1}(\mathbb{R}^d \times \mathbb{R}_+; \mathbb{R})$, we set

$$\begin{aligned} V_t =& \frac{\partial V}{\partial t}, \quad V_x = \left(\frac{\partial V}{\partial x_1}, \cdots, \frac{\partial V}{\partial x_2}\right) \\ V_{xx} =& \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_{d\times d} = \begin{pmatrix} \frac{\partial^2 V}{\partial x_1 \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_1 \partial x_d} \\ \vdots & & \vdots \\ \frac{\partial^2 V}{\partial x_d \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_d \partial x_d} \end{pmatrix} \end{aligned}$$

We are ready to state the first statement for Ito's formula.

Theorem 2.1.6. *Let $X(t)$ be a one-dimensional Itô process on $t \geq 0$ with the stochastic differential*

$$dX(t) = f(t)dt + g(t)dW(t).$$

where $f \in \mathcal{L}^1(\mathbb{R}_+; \mathbb{R})$ and $g \in \mathcal{L}^2(\mathbb{R}_+; \mathbb{R})$. Let $V \in C^{2,1}(\mathbb{R} \times \mathbb{R}_+; \mathbb{R})$. Then $V(X(t), t)$ is again an Itô process with the stochastic differential given by

$$\begin{aligned} dV(X(t),t) =& [V_t(X(t),t) + V_x(X(t),t)f(t) + \frac{1}{2}V_{xx}(X(t),t)g^2(t)]dt \\ &+ V_x(X(t),t)g(t)dW(t). \end{aligned} \tag{2.4}$$

Equation (2.4) is called *Itô 's formula* and has the following integral form

$$\begin{aligned} V(X(t),t) - V(X(0,0)) =& \int_0^t [V_t(X(s),s) + V_x(X(s),t)f(s) + \frac{1}{2}V_{xx}(X(s),s)g^2(s)]ds \\ &+ \int_0^1 V_x(X(s),s)g(s)dW(s). \end{aligned} \tag{2.5}$$

We are going to extend Definition 2.1.5 and the formula (2.4) to the multi-dimensional case. Let $W(t) = (W_1(t), ..., W_m(t))^T$, $t \geq 0$ be an m-dimensional Wiener process on the probability space $(\Omega, \mathcal{F}_t, \mathbb{P})$ and let $trace(A)$ be the sum of the elements of the main diagonal of an $n \times n$ square matrix A.

Definition 2.1.7. *A d-dimensional Itô process is an $\mathbb{R}^d$-valued continuous adapted process $X(t) = (X_1(t), ..., X_d(t))^T$ on $t \geq 0$ of the form*

$$X(t) = X(0) + \int_0^t f(s)ds + \int_0^t g(s)dW(s)$$

where $f = (f_1, ..., f_d)^T \in \mathcal{L}^1(\mathbb{R}_+; \mathbb{R}^d)$ and $g = (g_{ij})_{d\times m} \in \mathcal{L}^2(\mathbb{R}_+; \mathbb{R}^{d\times m})$.

Theorem 2.1.8. *Let $X(t)$ be a d-dimensional Itô process on $t \geq 0$ with the stochastic differential*

$$dX(t) = f(t)dt + g(t)dW(t)$$

where $f \in \mathcal{L}^1(\mathbb{R}_+; \mathbb{R}^d)$ and $g \in \mathcal{L}^2(\mathbb{R}_+; \mathbb{R}^{d\times m})$. Let $V \in C^{2,1}(\mathbb{R}^d \times \mathbb{R}_+; \mathbb{R})$. Then $V(X(t), t)$ is again an Itô process with the stochastic differential given by

$$\begin{aligned} dV(X(t),t) =& [V_t(X(t),t) + V_x(X(t),t)f(t) + \frac{1}{2}trace(g^T(t)V_{xx}(X(t),t)g(t))]dt \\ &+ V_x(X(t),t)g(t)dW(t). \end{aligned} \tag{2.6}$$

Example 2.1.9. *Let X(t) be a d-dimensional Ito process as given by Definition 2.1.5. Let Q be a $d \times d$ matrix. Then*

$$\begin{aligned} X(t)^TQX(t) - X^T(0)QX(0) =& \int_0^1 [X^T(s)(Q+Q^T)f(s) + \frac{1}{2}trace(g^T(s)(Q+Q^T)g(s))]ds \\ &+ \int_0^1 X^T(s)(Q+Q^t)g(t)dW(s). \end{aligned} \tag{2.7}$$

2.1.3 Existence and uniqueness of solutions of SODEs

Consider the d-dimensional stochastic ordinary differential equation (SODE) of Itô type

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW(t), \quad t \in [0, T], \tag{2.8}$$

with initial condition

$$X(0) = X_0,$$

where W is an m-dimensional Wiener process and $f : [0, T] \times \mathbb{R}^d \to \mathbb{R}^d$ and $g : [0, T] \times \mathbb{R}^d \to \mathbb{R}^{d\times m}$. We now present the definition of solution of equation (2.8).

Definition 2.1.10. *A solution $X(t)$ of (2.8) is an Itô process which satisfies the integral equation*

$$X(t) = X_0 + \int_0^t f(s, X(s))ds + \int_0^t g(s, X(s))dW(s) \quad t \in [0, T] \tag{2.9}$$

where $f \in \mathcal{L}^1([0,T], \mathbb{R}^d)$ and $g \in \mathcal{L}^2([0,T], \mathbb{R}^{d\times m})$ and $X(0) = X_0$ is the initial condition. A solution is said to be unique if any other solution $\tilde{X}$ is stochastically indistinguishable from $X(t)$, that is

$$\mathbb{P}\{X(t) = \tilde{X}(t) \text{ for all } 0 \le t \le T\} = 1.$$

If the diffusion coefficient g is independent of the solution $X(t)$, the SODE is said to have additive noise. If g depends on the solution $X(t)$, we say that an SODE has multiplicative noise. An SODE may not have a unique solution. We further present several theorems providing the conditions that guarantee the existence and uniqueness of the solution to equation (2.8) [23].

Theorem 2.1.11. *Assume there exist two positive constants C_1 and C_2 such that*

- *(Lipschitz condition) For all $x, y \in \mathbb{R}^d$ and $t \in [0, T]$*

$$max(|f(t,x) - f(t,y)|^2, |g(t,x) - g(t,y)|^2) \le C_1|x - y|^2, \tag{2.10}$$

- *(Linear growth condition) For all $(x, t) \in \mathbb{R}^d \times [0, T]$*

$$max(|f(t,x)|^2, |g(t,x)|^2) \le C_2(1 + |x|^2). \tag{2.11}$$

Then there exist a unique solution $X(t)$ to equation (2.8).

The next theorem is a generalisation of Theorem 2.1.11 in which the global Lipschitz condition, which is often too restrictive, is replaced by a local Lipschitz condition.

Theorem 2.1.12. *Assume that f, g in equation (2.8) satisfy the following conditions*

- *(Local Lipschitz condition) For every integer $n \ge 1$, there exist a positive constant K_n such that, for all $x, y \in \mathbb{R}^d$ and $t \in [0, T]$ with $max(|x|, |y|) \le n$*

$$max(|f(t,x) - f(t,y)|^2, |g(t,x) - g(t,y)|^2) \le K_n|x - y|^2. \tag{2.12}$$

- *(Linear growth condition) There exist a positive constant C such that for all $(x, t) \in \mathbb{R}^d \times [0, T]$*

$$max(|f(t,x)|^2, |g(t,x)|^2) \le C(1 + |x|^2). \tag{2.13}$$

Then there exists a unique solution $X(t)$ to equation (2.8).

Is important to notice that the local Lipschitz condition allows us to include functions as the coefficients f and g, *e.g.*, functions that have continuous partial derivatives of first order with respect to $(x,t) \in \mathbb{R}^d \times [0,T]$. The linear growth condition still excludes some important functions like $-|x|^2x$ as the coefficients of (2.8). It is possible to obtain an improvement by replacing the linear growth condition with a monotone one [23].

Theorem 2.1.13. *Assume that f, g in equation (2.8) satisfy the following conditions*

- *(Local Lipschitz condition) For every integer $n \geq 1$, there exist a positive constant K_n such that, for all $x, y \in \mathbb{R}^d$ and $t \in [0,T]$ with $max(|x|,|y|) \leq n$*

$$max(|f(t,x) - f(t,y)|^2, |g(t,x) - g(t,y)|^2) \leq K_n|x-y|^2. \tag{2.14}$$

- *(Monotone condition) There exists a positive constant C such that for all $(x,t) \in \mathbb{R}^d \times [0,T]$*

$$x^T f(t,x) + \frac{1}{2}|g(t,x)|^2) \leq C(1+|x|^2). \tag{2.15}$$

Then there exists a unique solution $X(t)$ to equation (2.8).

It is important to notice that the solution $X(t)$ found above is called a *strong* solution, because the probability space, the Wiener process, the filtration and the coefficients are all given in advance and then the solution is constructed. If we are only given the functions f and g and we are free to select a Wiener process and then find a solution $X(t)$ corresponding to this particular Wiener process, then the solution $X(t)$ is called a *weak* solution. Furthermore the weak uniqueness simply means that any two solutions (weak or strong) are identical in law, *i.e.*, have the same finite-dimensional distributions. It is evident that a strong solution is also a weak solution, but the converse is not true in general ([24], p. 71).

2.2 Stochastic Delay Differential Equations (SDDEs)

2.2.1 General theory

Delay differential equations (DDEs) give a mathematical formulation of problems with time-lag or after-effect. In such cases the rate of change of a system depends not only

on the present but also on the past states of the system. They have a wide range of applications in physics, engineering, biology and economics. The large applicability of these systems is due to the fact that the reaction of real-world to external input is not always instantaneous and it needs some time, which can be translated into a mathematical language by the introduction of some delay terms. A complete introduction to the theory of DDEs and their application to the natural sciences is given by [28], where the authors also provide several examples. Considering stochastic effects, by the introduction of some kind of noise in DDEs, we are led to Stochastic Delay Differential Equations (SDDEs). These stochastic models are attracting an increasing interest in many different disciplines. For example, in biology there are applications of SDDEs to infectious diseases [5], bacteriophage infection [29] and in a recent paper [7], to virus tumor immune system. For various aspects of the theory of SDDEs (or equivalently named SFDEs, *i.e.*, Stochastic Functional Differential Equations) we refer to [30, 31] and for references concerning the applications in different disciplines see the introduction in [32].

A general functional differential equation with time lag has the form

$$dx(t) = f(t, x_t)dt$$

where $x_t : [-\tau, 0] \to \mathbb{R}^d$; $x_t(\theta) := x(t+\theta)$, for every $\theta \in [-\tau, 0]$. Considering the stochastic case, we obtain the SDDE

$$dX(t) = f(t, X_t)dt + g(t, X_t)dW(t), \tag{2.16}$$

where X_t is a stochastic process such that $X_t(\theta) := X(t+\theta)$, for $\delta \in [-\tau, 0]$, and W is an m-dimensional Wiener process. The history functional X_t provides a very general description of the dependence on the past. Depending on the choice of the memory terms, we may sort the SDDEs into different classes. We give three common and important types of memory. If we set f and/or g to be of the form

$$H(s, X(s), X(s-\tau)),$$

$$H(s, X(s), X(s-\tau(s))$$

or

$$H(s, X(s), \int_{-\tau}^{0} K(s, \theta, X(s+\theta))d\theta) = H(s, X(s), \int_{t-\tau}^{t} K(s, t-\theta, X(s))d\theta)$$

then we call equation (2.16) an SDDE with *discrete*, *variable* or *distributed* delay term, respectively.

2.2.2 Existence and uniqueness of solution

Let $(\Omega, \mathcal{F}, \mathbb{P})$ be a complete probability space with filtration $\mathcal{F}_t \geq 0$ and $W(t)$ be an m-dimensional Wiener process defined on this space. Let $\tau > 0$ and denote by $\mathcal{C}[-\tau, 0]$ the family of continuous functions $\varphi : [-\tau, 0] \to \mathbb{R}^d$ endowed with the norm $\|\varphi\| = \sup_{-\tau \leq \theta \leq 0} |\varphi(\theta)|$. Consider the equation

$$dX(t) = f(t, X_t)dt + g(t, X_t)dW(t) \tag{2.17}$$

where $f : \mathcal{C}([-\tau, 0]; \mathbb{R}^d) \times [t_0, T] \to \mathbb{R}^d$ and $g : \mathcal{C}([-\tau, 0]; \mathbb{R}^d) \times [t_0, T] \to \mathbb{R}^{d \times m}$ are measurable functions. The *segment process* X_t, which for fixed $\tau > 0$, is defined as

$$X_t(\theta) := X(t+\theta)\ \theta \in [-\tau, 0]$$

is regarded as a $\mathcal{C}([-\tau, 0], \mathbb{R}^d)$-valued stochastic process and the initial condition is

$$X_0 = \xi \tag{2.18}$$

where $\xi = \{\xi(\theta) : -\tau \leq \theta \leq 0\}$ is a $\mathcal{F}_{t_0}$-measurable, $\mathcal{C}([-\tau, 0], \mathbb{R}^d)$-valued stochastic process such that $\mathbb{E}\|\xi\|^2 < \infty$. So the initial value-problem for the SDDE is to find the solution of equation (2.17) satisfying this initial data (2.18). As was done for SODEs, it is necessary to define what a solution is and what the conditions of existence and uniqueness for a solution are.

Definition 2.2.1. *An $\mathbb{R}^d$-valued Itô process $X(t)$ on $-\tau \leq 0 \leq T$ is called a solution to equation (2.17) with initial data (2.18) if $X_0 = \xi$ and for every $0 \leq t \leq T$ $X(t)$ satisfies the integral equation*

$$X(t) = X(0) + \int_0^t f(s, X_s)ds + \int_0^t g(s, X_s)dW(s) \quad a.s. \tag{2.19}$$

where $f \in \mathcal{L}^1([0, T], \mathbb{R}^d)$ and $g \in \mathcal{L}^2([0, T], \mathbb{R}^{d \times m})$. A solution is said to be unique if any other solution $\tilde{X}$ is stochastically indistinguishable from $X(t)$, that is

$$\mathbb{P}\{X(t) = \tilde{X}(t) for\ all - \tau \leq t \leq T\} = 1.$$

Theorem 2.2.2. *Assume there exist two positive constants C_1 and C_2 such that*

- *(Uniform Lipschitz condition) For all $\phi, \psi \in C([-\tau, 0]; \mathbb{R}^d)$ and $t \in [0, T]$*

$$max(|f(t,\phi) - f(t,\psi)|^2, |g(t,\phi) - g(t,\psi)|^2) \leq C_1 \|\phi - \psi\|^2. \tag{2.20}$$

- *(Linear growth condition) For all $(\phi, t) \in C([-\tau, 0]; \mathbb{R}^d) \times [0, T]$*

$$max(|f(t,\phi)|^2, |g(t,\psi)|^2) \leq C_2(1 + \|\phi\|^2). \tag{2.21}$$

Then there exists a unique solution $X(t)$ to equation (2.17).

As seen in the last section for SODEs, the uniform Lipschitz condition is in some sense quite restrictive. There exists a generalisation of Theorem 2.2.2 where the global Lipschitz condition is replaced by a local one [23].

Theorem 2.2.3. *Assume that f, g in equation (2.17) satisfy the following conditions*

- *(Local Lipschitz condition) For every integer $n \geq 1$, there exists a positive constant K_n such that, for all $\phi, \psi \in C([-\tau, 0]; \mathbb{R}^d)$ and $t \in [0, T]$ with $max(\|\phi\|, \|\psi\|) \leq n$*

$$max(|f(t,\phi) - f(t,\psi)|^2, |g(t,\phi) - g(t,\psi)|^2) \leq K_n \|\phi - \psi\|^2. \tag{2.22}$$

- *(Linear growth condition) There exist a positive constant C such that for all $(\phi, t) \in C([-\tau, 0]; \mathbb{R}^d) \times [0, T]$*

$$max(|f(t,\phi)|^2, |g(t,\psi)|^2) \leq C(1 + \|\phi\|^2). \tag{2.23}$$

Then there exists a unique solution $X(t)$ to equation (2.17).

If we consider equation (2.17) on $t > 0$ and the assumptions of Theorem 2.2.3 to hold on every subinterval $[0, T]$ of $[t, \infty]$, then equation (2.17) has a unique solution $X(t)$ on the entire interval $[-\tau, \infty]$. Such a solution is called a *global* solution. However, if we remove the linear growth condition but keep the local Lipschitz condition, then the SDDE may not have global solutions. In this case it is necessary to define *local* solutions (see [23], p. 154).

3

Stability theory for SODEs and SDDEs

In this chapter we provide an overview of stochastic stability theory. We introduce the most commonly used definitions of stability for stochastic differential equations, with and without delay. Then we describe the main results of stochastic stability. In the last part of this chapter we depict the problem of constructing a suitable stability theory in the first approximation for stochastic delay differential equations, that will be studied in the next chapter.

3.1 Stability of equilibria for SODEs

The concept of stability of an equilibrium of a differential equation concerns the property to change slightly under slight perturbations in the initial data. The concept of stability for a dynamical system was introduced by A.M. Lyapunov in 1892 [33]. He also developed a method for determining the stability behaviour without solving the equation, the well known *Lyapunov direct or second method*. For the theory of stability of deterministic systems we refer to the books by Hahn [34], Krasovskii [35] and Lakshmikantham *et al.* [36]. In this section we present the fundamental notions of stability theory for Itô equations. Stability analysis for stochastic differential equations was began in 1960 by Kac and Krasovskii [9]. They investigated the stability of the null solution $X(t) = 0$ of a random equation in terms of Lyapunov functions, considering, essentially, instead of the derivative $\frac{dV}{dt}$ along the sample path, the expectation

of this derivative. Inspired by this paper, Hasminskii in [10] proved several theorems, improving the theory of stochastic stability for differential equations.

Let us consider the d-dimensional Itô equation (2.8) and assume that it admits the trivial solution $X(t) = 0$. It is possible to have different statements of stability depending on the particular concept of "slight variation of the solution". The most commonly used definitions of stochastic stability are those of *stability in p-th mean, stability in probability* and *almost sure stability*. In the following, we assume that equation (2.8)) satisfies the assumptions of the existence and uniqueness theorems studied in the last chapter and that $f(t;0) = g(t;0) = 0 \quad$ for $t \geq 0$ such that the trivial solution $X(t) = 0$ holds for $X_0 = 0$.

3.1.1 Stability in p-th mean

We recall in this section the definitions and some results concerning p-stability [37]. We will denote a solution of (2.8) starting at t_0 and with initial function X_0 by $X(t; t_0, X_0)$.

Definition 3.1.1. *The trivial solution $X(t) \equiv 0$ of (2.8) is called*

- p-stable $(p > 0)$ *if, for each $\epsilon > 0$ there exists $\delta(\epsilon) > 0$ such that, for $\|X_0\| < \delta(\epsilon)$ the following inequality holds*

$$\mathbb{E}(|X(t; 0, X_0)|^p) \leq \epsilon \quad \forall t \in [0, T].$$

- asymptotically p-stable *if it is p-stable and moreover*

$$\mathbb{E}(|X(t; 0, X_0)|^p) \to 0 \text{ as } t \to \infty$$

- exponentially p-stable $(p > 0)$ *if there exist positive constants C_1, C_2 such that*

$$\mathbb{E}(|X(t; 0, X_0)|^p) \leq C_1 |X_0|^p \exp(-C_2 t).$$

The case of p-stability most frequently studied in the literature is for $p = 1$ (stability in the mean) and for $p = 2$ (stability in the mean square). If $p = 2$, the trivial solution of (2.8) is said to be *exponentially mean-square stable*.

The following theorem gives sufficient conditions for exponential p-stability of the stochastic system (2.8) in terms of Lyapunov functions [10]. Let $\mathcal{U}$ be the set $\mathcal{U} = [0, T] \times \mathbb{R}^d$, $T > 0$. Hence $V \in C_2^0(\mathcal{U})$ is a twice continuously differentiable function with respect to X and a continuous function with respect to t.

Theorem 3.1.2. *Suppose there exists a function* $V(t, X(t)) \in C_2^0(\mathcal{U})$ *for which the generating operator* LV *from* $[0, \infty) \times C([-\tau, 0]; \mathbb{R}^d)$ *to* $\mathbb{R}$ *defined by*

$$LV(t, X(t)) = \frac{\partial V(t, X(t))}{\partial t} + f^T \frac{\partial V(t, X(t))}{\partial X(t)} + \frac{1}{2} trace \left[g^T \frac{\partial^2 V(t, X(t))}{\partial X(t)^2} g \right],$$

satisfies the inequalities

$$K_1 |X(t)|^p \leq V(t, X(t)) \leq K_2 |X(t)|^p \tag{3.1a}$$

$$LV(t, X(t)) \leq -K_3 |X(t)|^p, \quad K_i > 0, \quad p > 0. \tag{3.1b}$$

Then the trivial solution of (2.8) *is* exponentially p-stable *for* $t \in [0, T]$. *If in inequalities* (3.1) *we have* $p = 2$, *the trivial solution of* (2.8) *is said to be* exponentially mean-square stable.

The function $V(t, X(t))$ used in the theorem above is called a *stochastic Lyapunov function*. There also exist necessary conditions for exponential p-stability in terms of Lyapunov functions. For the proof we refer to [10].

Theorem 3.1.3. *If the trivial solution of* (2.8) *is exponentially* p*-stable and the coefficients* f *and* g *have continuous bounded derivatives with respect to* X *up to second order, then there exists a function* $V(t, X(t)) \in C_2^0(\mathcal{U})$ *satisfying inequalities* (3.1) *and also*

$$\left| \frac{\partial V(t, X(t))}{\partial X(t)} \right| < K_4 |X(t)|^{p-1}, \qquad \left| \frac{\partial^2 V(t, X(t))}{\partial X(t)^2} \right| < K_4 |X(t)|^{p-2} \tag{3.2}$$

for some $K_4 > 0$.

The use of these theorems depends on the being able to construct a suitable Lyapunov function $V(t, X(t))$. There are several procedures to construct suitable functions. In 1995 the general method of Lyapunov functionals construction was proposed by Kolmanovskii and Shaikhet for stochastic functional-differential equations and developed later consistently for stochastic difference equations with discrete time and continuous time [11, 12]. Unfortunately, every construction of Lyapunov functionals is always related to the form of the equation under stability analysis, which means that it could be difficult when the SDDEs are quite complicated (*e.g.*, nonlinear systems, several parameters involved, order bigger than one,...).

3.1.2 Stability in probability

In this section we give the definition of stability in probability for SODEs.

Definition 3.1.4. *The trivial solution of* (2.8) *is called*

- stable in probability *if for all* $t, s \geq 0$ *and* $\epsilon > 0$ *the relationship*

$$\lim_{X_0 \to 0} \mathbb{P}\left\{\sup_{t \geq s} |X(t; 0, X_0)| > \epsilon\right\} = 0$$

  holds.

- uniformly stable in probability *if for all* $t \geq 0$ *and* $\epsilon > 0$ *the relationship*

$$\lim_{X_0 \to 0} \mathbb{P}\left\{\sup_{t \geq s} |X(t; 0, X_0)| > \epsilon\right\} = 0 \qquad \textit{uniformly in } s \geq 0$$

  holds.

- asymptotically stable in probability *if it is stable in probability and for all initial conditions* $X(0) = X_0$ *the relationship*

$$\mathbb{P}\left\{\lim_{t \to \infty} X(t; 0, X_0) = 0\right\} = 1$$

  holds.

The definition of stability in probability involves the overall behaviour of the sample functions X on the interval $[0, \infty]$. The exponential p-stability implies a *weak stability in probability* given by

$$\lim_{X_0 \to 0} \mathbb{P} \sup_{t \geq s} \{|X(t; 0, X_0)| > \epsilon\} = 0.$$

For an autonomous linear equation, the two concepts are, however, equivalent. There exist several results regarding the implications between the different types of stability and the additional conditions required in order to deduce one from the other. We do not wish to say more about this here, but for an interested reader we refer to [10].

The following theorems give conditions for stability in probability.

Theorem 3.1.5. *Suppose there exists a Lyapunov function* $V(t, X(t)) \in C_2^0(\mathcal{U})$ *for which the generating operator is*

$$LV(t, X(t)) = \frac{\partial V(t, X(t))}{\partial t} + f^T \frac{\partial V(t, X(t))}{\partial X(t)} + \frac{1}{2} trace\left[g^T \frac{\partial^2 V(t, X(t))}{\partial X(t)^2} g\right],$$

such that for any $X(t) = 0$ *there exists a positive constant* C_1 *such that the inequalities*

$$C_1(|X(t)|) \leq V(t, X(t)), \tag{3.3a}$$
$$LV \leq 0 \tag{3.3b}$$

*hold (*i.e.*,* V *is positive definite in Lyapunov's sense). Then the trivial solution of* (2.8) *is* stable in probability *for* $t \in [0, T]$.

Theorem 3.1.6. *Suppose there exists a Lyapunov function* $V(t, X(t))$ *satisfying the conditions* (3.3)*) of Theorem 3.1.5 in the domain* $\mathfrak{U}$ *such that there exist positive constants* C_1, C_2 *and* C_3 *such that*

$$C_1(|X(t)|) \leq V(t, X(t)) \leq C_2(|X(t)|), \tag{3.4a}$$
$$LV \leq -C_3(|X(t)|). \tag{3.4b}$$

Then the trivial solution of (2.8) *is* asymptotically stable in probability.

We will make use of these results in the next paragraph, where we will recall a theorem of first approximation for SODEs.

3.1.3 Stability in the first approximation

Given nonlinear systems, it is possible to reduce the study of stability to the linearised versions around the equilibrium point, obtained from the original systems by dropping terms of higher than first order. The first result in this direction was obtained by Kac and Krasovskii [35] for studying randomly perturbed systems. Similar results were proved by Gihman [38] for diffusion-type processes. We mention also the stochastic version of the Hartman-Grobman theorem in random dynamical theory [39]. We recall one of the theorems of first approximation for Itô equations obtained by Hasminskii in [10].

Theorem 3.1.7. *Consider the nonlinear system*

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW(t). \tag{3.5}$$

If the linearised version of (3.5) *is exponentially p-stable for some* $p > 0$ *and the derivatives of the drift and diffusion coefficients are bounded and uniformly (in* t*) continuous in* X *for* $X = 0$*, then the system* (3.5) *is asymptotically stable in probability.*

3.2 Stability of equilibria for SDDEs

In this paragraph we give the definitions of stability of the equilibrium point X^* of the SDDE system (2.17). We will denote a solution of (2.17) starting at t_0 and with initial function ϕ by $X(t;t_0,\phi)$. Assume furthermore that $f(t,0) = g(t,0) = 0$ so equation (2.17) admits the trivial solution $X(t) \equiv 0$.

Definition 3.2.1. *The trivial solution $X(t) \equiv 0$ of SDDE (2.17) is termed (1)* locally mean-square stable*, if for each $\epsilon > 0$, there exists $\delta \geq 0$ such that $\mathbb{E}(\|\phi\|^2) < \delta$ implies*

$$\mathbb{E}(|X(t;t_0,\phi)|^2) < \epsilon, \qquad \textit{for} \quad t \geq t_0;$$

(2) locally asymptotically mean-square stable*, if it is locally mean-square stable and if there exists $\delta \geq 0$ such that $\mathbb{E}(\|\phi\|^2) < \delta$ implies*

$$\mathbb{E}(|X(t;t_0,\phi)|^2) \to 0 \qquad \textit{as} \quad t \to \infty;$$

(3) locally exponentially mean-square stable (with exponent ν^+) *if it is locally mean-square stable and if there exists a $\delta \geq 0$ such that, whenever $\mathbb{E}(\|\phi\|^2) < \delta$, there exists some finite constant C and $\nu^+ > 0$ such that*

$$\mathbb{E}(|X(t;t_0,\phi)|^2) \leq C\ \mathbb{E}(\|\phi\|^2)\ \exp(-\nu^+(t-t_0)) \quad (t_0 \leq t < \infty).$$

If, in the above, δ may be taken to be arbitrarily large then the stability is in each case global *rather than local.*

3.2.1 Asymptotic p-stability

By generalisation of Lyapunov's direct method it is possible to obtain sufficient conditions for asymptotic stability of equilibria for SDDEs. The following theorem was obtained by Kolmanovskii and Nosov in 1986. For the proof we refer to [16].

Theorem 3.2.2. *Let $p \geq 2$ and C_1, C_2 and C_3 be positive constants. Assume that there is a continuous functional $V : [0,\infty) \times C([-\tau,0];\mathbb{R}^d) \to \mathbb{R}$ such that*

$$C_1|\phi(0)| \leq V(t,\phi) \leq C_2\|\phi\|^p, \qquad t \geq 0 \tag{3.6}$$

and

$$\mathbb{E}V(t_2, X(t_2)) - \mathbb{E}V(t_1, X(t_1)) \leq -C_3 \int_{t_1}^{t_2} \mathbb{E}|X(s)|^p ds, \quad 0 \leq t_1 \leq t_2 < \infty. \tag{3.7}$$

Then the trivial solution of (2.17) *is asymptotically p-stable.*

Theorem 3.2.2 provides a very general framework to study stability properties of SDDEs. However, it is often difficult to find a suitable functional in practice, even more than finding a Lyapunov function in the SODE case.

3.2.2 Exponential p-stability

Developing a method used by Razumikhin in [13, 14] for ordinary differential equations, in 1996 Mao obtained the following theorem on exponential p-stability for SDDEs [15].

Theorem 3.2.3. *Let λ, p, C_1, C_2 all be positive constants and $q > 1$. Assume that there exists a function $V \in C^{1,2}([-\tau, \infty] \times \mathbb{R}^d; \mathbb{R}+)$ such that*

$$C_1|X|^p \leq V(t, X(t)) \leq C_2|X|^p \tag{3.8}$$

and moreover

$$\mathbb{E}LV(t, \psi) \leq -\lambda \mathbb{E}V(t, \psi(0)) \tag{3.9}$$

for all $t \geq 0$ and those $\psi \in L^p([-\tau, 0]; \mathbb{R}^d)$ satisfying

$$\mathbb{E}V(t + \theta, \psi(\theta)) < q\mathbb{E}V(t, \psi(0)) \qquad on - \tau \leq \theta \leq 0.$$

Then for all $\xi \in C^b([-\tau, 0]; \mathbb{R})$

$$\mathbb{E}|X(t, \xi)|^p \leq \frac{C_2}{C_1}\mathbb{E}\|\xi\|^p \exp(-\gamma(t - t_0)) \quad on\ t \geq 0 \tag{3.10}$$

where $\gamma = min(\lambda, log(q)/\tau)$.

For nonlinear equations, stability of equilibrium solutions (either trivial or not) can be investigated by the method of "stability in the first approximation", but results in this direction for SDDEs are not as developed as in the case of SDEs. There exists a theorem stated for the case in which the equation of the first approximation of (2.17) is a deterministic one

$$dx(t) = f(t, x_t), \qquad t > 0, x \in \mathbb{R}^d \tag{3.11}$$

where $x_t = x(t+\theta)$ and continuous functionals $f(t,\phi)$, $g(t,\phi)$ satisfy the conditions

$$|f(t,\phi) - f(t,\phi_1)| \leq L_1\|\phi - \phi_1\|, \qquad f(t,0) = g(t,0) = 0 \tag{3.12}$$

$$|g(t,\phi) - g(t,\phi_1)| \leq L_1\|\phi - \phi_1\|, \qquad \phi, \phi_1 \in C([-\tau, 0], \mathbb{R}^d) \tag{3.13}$$

From theorems developed in the deterministic theory, Kolmanovskii and Nosov proved the following result [16].

Theorem 3.2.4. *Let the condition*

$$\mathbb{E}\exp 2\left[-C_4 t/C_2 + C_3 L/C_1 \int_0^t |\xi(s)|ds\right] \leq \exp(-\beta t), \qquad \beta \geq 0 \tag{3.14}$$

be satisfied (where the constants C_1, C_2, C_3 and C_4 derive from deterministic theory) and the trivial equation of (3.11) be uniformly exponentially stable. Then the trivial solution of (2.17) is asymptotically mean-square stable.

In the next chapter we will to obtain results for stability in the first approximation for nonlinear SDDEs where the linearised equations are still SDDEs.

4

Stability of stochastic integro-differential equations with distributed memory terms

The purpose of this chapter is to construct an original first approximation theory for stochastic delay differential equations not previously existent. In the first and second section of this chapter we focus our attention on the proof of comparison theorems, obtaining a new comparison theorem which guarantees the exponential mean square stability for the equilibrium of stochastic differential equations with distributed memory terms using a generalisation of the Halanay inequality. In the third section we prove our new mean square stability theorems for SDDEs, providing at the end an original theorem of stability in the first approximation for SDDEs, which will be applied in the next chapter.

4.1 Introduction and motivation

We shall investigate the mean-square asymptotic stability of an equilibrium of a non-linear stochastic delay system with distributed memory terms of the form

$$\begin{aligned} dX(t) = \quad & F\left(t, X(t), \int_{-\tau}^{0} K(t,s,X(t+s)ds)\right)dt \\ & +G\left(t, X(t), \int_{-\tau}^{0} K(t,s,X(t+s)ds)\right)dW(t) \end{aligned} \tag{4.1}$$

with initial data

$$X(s) = \phi(s) \qquad s \in J := [-\tau, 0], \quad \tau > 0.$$

This system can be regarded as the noise perturbed deterministic integro-differential system

$$dX(t) = f\left(t, X(t), \int_{-\tau}^{0} K(t, s, X(t+s)ds)\right) dt. \tag{4.2}$$

The discussion of the stability for a deterministic system (4.2) was well studied by many authors. For a general treatment of stability properties, numerical study and applications of this kind of equations we refer to the work of Baker and Tang [40].

Let $\{\Omega, \mathcal{F}, \mathbb{P}\}$ be a complete probability space with the filtration $\{\mathcal{F}_t\}_{t\in[0,T]}$ that should be increasing, right-continuous and such that each $\mathcal{F}_t$, $t \in [0, T]$, contains all $\mathbb{P}$-null sets in $\mathcal{F}$. Let $W(t) = (W_1(t), \ldots, W_m(t))^T$ be an m-dimensional Wiener process (or Brownian motion) on that probability space.

Throughout this chapter we will use the following notation to refer to equation (4.1)

$$dX(t) = F\left(t, X(t), Y(t)\right) dt + G\left(t, X(t), Y(t)\right) dW(t) \tag{4.3}$$

where

$$Y(t) = \int_{-\tau}^{0} K(t, s, X(t+s)ds).$$

We denote the Euclidean norm in $\mathbb{R}^d$ by $|.|$ and the mean-square norm of a vector-valued square-integrable random variable $Z \in L_2(\Omega; \mathbb{R}^d)$ by $\|Z\|_{L_2} := (\mathbb{E}\,|Z|^2)^{1/2}$, where $\mathbb{E}$ is expectation with respect to $\mathbb{P}$. Let $C[-\tau, 0] = \{\varphi : [-\tau, 0] \to \mathbb{R}^d\}$ be the space of continuous functions with the norm $\|\varphi\| = \sup_{-\tau\le\theta\le 0} |\varphi(\theta)|$.

We assume that the drift and diffusion coefficients $F : [0, T] \times \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}^d$, $G : [0, T] \times \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}^{d\times m}$, $j = 1, \ldots, m$, are continuous.

We denote by $X(t; t_0, \phi)$ a solution depending on the initial time t_0 and initial data ϕ. We are going to define the following conditions.

Condition C_0 $\phi : J \times \Omega \to \mathbb{R}$ satisfies $\mathbb{E}(\|\phi(t)\|^2) < \infty$; almost all sample path are continuous and $\phi(t)$ is independent of the σ-algebra generated by $W(t)$.

Condition C_1 There exists a path-wise unique strong solution $X(t) \equiv X(t; t_0, \phi)$ of equation (4.3) and $\mathbb{E}(\|X((s; t_0, \phi))\|^2) < \infty$.

As shown in Chapter 2, sufficient assumptions guaranteeing condition C_1 are that F and G are continuous, that F and G satisfy, on their domain of definition,uniform Lipschitz conditions, and that F and G satisfy a linear growth condition, along with the condition C_0. Weaker conditions include local Lipschitz conditions, as proved in [23]. In [41] it is possible to find some conditions under which is still satisfied the condition C_1 when the coefficients of equation (4.3) do not satisfy the linear growth condition, though they satisfy local Lipschitz conditions. Theorem 2.1 in [41] shows that if the deterministic model has a global positive solution, then the corresponding SDDE will have a global positive solution, too. Also a generalized existence and uniqueness theorem which covers a wider class of nonlinear SFDEs is proved in [42]. In a recent paper by Max von Renesse [43] is showed that monotonicity of the coefficient guarantees local existence of the solution of SFDEs.
We will suppose that the equation (4.3) admits the solution $X(t) \equiv 0$ for $(t \geq t_0 - \tau)$ (called *trivial solution*), and to this end we request that the following condition holds.

Condition C_2 F and G satisfy $F(t, 0, 0) = 0$ and $G(t, 0, 0) = 0$, for $t \geq t_0$.

Our aim is to analyse the stability of a nonlinear system (4.3) by studying the stability properties of the linearisation in the first approximation. This chapter divides into two parts. In the first part we state, using Halanay's inequalities, comparison results useful in the investigation of exponential mean square stability of linear stochastic delay differential systems with distributed memory terms. In the second part we obtain conditions under which the asymptotic mean square stability of a non linear system (4.3) is implied by the mean square exponential stability of the SDDE linearised system in the first approximation.

4.2 Comparison stability theorems

The aim of this section is to obtain the conditions to guarantee the asymptotic mean-square stability for the equilibrium of SDDEs with distributed memory terms using a generalisation of the Halanay inequality. First of all we give a brief outline of using Halanay's inequality to study stability of deterministic differential equations. For a detailed overview of applying Halanay-type inequalities in the analysis of deterministic delay differential equations we refer to [44].

4.2.1 Halanay's inequalities

In [45] Halanay used the inequality to study the stability of the zero solution of a system of the form

$$\dot{x}(t) = Ax(t) + Bx(t-\tau)$$

deducing stability from the corresponding property for the system

$$\dot{y}(t) = (A+B)y(t)$$

where $A + B < 0$. Consider a continuous function f, with f' being its right-hand derivative.

Lemma 4.2.1 (Halanay's inequality)**.** *Suppose that*

$$f(t)' \leq -Af(t) + B \sup_{t-\tau \leq s \leq t} f(s) \qquad \text{for} \quad t \geq t_0 \geq 0, A > B > 0. \tag{4.4}$$

Then there exists γ, $K > 0$ such that

$$f(t) \leq Ke^{-\gamma(t-t_0)} \qquad \text{for} \quad t \geq t_0 \geq 0 \tag{4.5}$$

and hence

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

Before to introduce a comparison theorem, we need to state the following comparison result [46].

Lemma 4.2.2. *Suppose that $\alpha, \beta, \tau \in \mathbb{R}$ with $\tau \geq 0$ and $0 < \beta < \alpha$. (a) The function*

$$\Omega(\nu) \equiv \Omega(\nu;\ \alpha, \beta, \tau) = \nu - \alpha + \beta \exp\{\nu\tau\} \tag{4.6}$$

has a single real zero ν^+ which is positive. If $\tau = 0$ then $\nu^+ = \alpha - \beta$; if $\tau > 0$ then $0 < \nu^+ < \alpha - \beta$. (b) For arbitrary $K > 0$, the positive monotonic-decreasing function

$$w_K(t) = K \exp\{-\nu^+(t-t_0)\} \quad (\text{defined for} \quad t \in \mathbb{R}), \tag{4.7}$$

satisfies

$$w_K'(t) = -\alpha w_K(t) + \beta w_K(t-\tau) \quad \text{for} \quad t \geq t_0. \tag{4.8}$$

Proof. a) For $\tau = 0$, $\mathcal{Q}(\nu) = \nu - \alpha + \beta$ and the result is obvious. Suppose, therefore, that $\tau > 0$. The existence of a zero ν^+ follows because $\mathcal{Q}(0) = -(\alpha - \beta) < 0$ and $\mathcal{Q}(\alpha) = \beta \exp(\alpha\tau) > 0$. Its uniqueness follows because the derivative $\mathcal{Q}'(\nu)$ is $1 + \beta\tau \exp(\nu\tau) > 0$. Obviously $0 < \nu^+ < \alpha$, a result, which we can now refine. Since $\mathcal{Q}(\alpha - \beta) = \beta(\exp((\alpha - \beta)\tau) - 1) > 0$ we have $\nu^+ \in (0, \alpha - \beta)$. b) By part a), for $0 < \beta < \alpha$ the unique real zero of $\mathcal{Q}(\nu)$ is a value $\nu^+ \in (0, \alpha - \beta]$. The validity of (4.8) can then be verified by substitution, employing the property $\mathcal{Q}(\nu^+;\ \alpha, \beta, \tau) = 0$. □

The following comparison result will be useful in the investigation of SDDEs. The presentation of Theorem 4.2.3 and the proof is taken from [46].

Theorem 4.2.3. *Let α, β and $\tau \geq 0$ be given constants in $\mathbb{R}$. Suppose that the positive-valued function $v : [t_0 - \tau, \infty) \to \mathbb{R}^+$, is continuous (on $[t_0 - \tau, \infty)$), for given $\tau \geq 0$. Assume, further, that*

$$0 \quad < \beta < \alpha, \tag{4.9}$$

$$D^+ v(t) \quad \leq \quad -\alpha\ v(t) \ +\ \beta \quad \sup_{s \in [t-\tau, t]} v(s),\ t \in [t_0, \infty). \tag{4.10}$$

Then

$$v(t) \leq \big\{ \sup_{s \in J} v(s) \big\}\ \exp\{-\nu^+(t - t_0)\} \quad \textit{for } t_0 \leq t < \infty, \tag{4.11}$$

where $\nu^+ \in (0, \alpha - \beta]$ is the zero of $\mathcal{Q}$ in Lemma 4.2.2.

Proof. The case where $\tau = 0$ is immediate, so let $\tau > 0$. By the *generalised mean-value theorem of differential calculus* we have that, let $u(\cdot)$ be real-valued and continuous function on $[t_0, T)$, if, for some interval I,

$$D^+ u(t) \in I \quad \text{for} \quad t \in J \setminus S,$$

then

$$\frac{u(b) - u(a)}{b - a} \in I, \quad \text{for } a, b \in J \text{ with } \ a = b,$$

where J denotes the interval $[t_0, T)$ and S denotes an at most countable subset of $[t_0, T)$. In particular: if $D^+ u(t) \geq 0$, or $D^+ u(t)0$ in $J \setminus S$, then u is monotonically increasing, or strictly monotonically increasing, respectively.

By this result, condition (4.10) implies

$$D_- v(t) \leq -\alpha\ v(t) \ +\ \beta \quad \sup_{s \in [t-\tau, t]} v(s),\ t \in (t_0, \infty). \tag{4.12}$$

Set $K = \sup_{s\in J} v(s)$ (by assumption, $K > 0$) in the definition of $w_K(t)$ above. Choose any $T > t_0$ and let $\ell > 1$ be arbitrary. The monotonic decreasing function $w_K(t)$ is differentiable on $[t_0 - \tau, T]$. The following inequality

$$v(t) < \ell w_K(t) \text{ for } t_0 - \tau \le t < T. \tag{4.13}$$

can be proved by contradiction. Obviously

$$v(t) < \ell w_K(t) \text{ when } t_0 - \tau \le t \le t_0.$$

In contradiction of (4.13), suppose that $v(t_\star) = \ell w_K(t_\star)$, for some arguments $t_\star \in (t_0, T)$. Since $v(t)$ and $w_K(t)$ are continuous functions, there must exist some *least* value $t_1 \in (t_0, T)$ such that

$$v(t) < \ell w_K(t) \quad \text{for } t_0 - \tau \le t < t_1 \quad \text{and} \quad v(t_1) = \ell w_K(t_1). \tag{4.14}$$

Observe that (4.14) implies

$$\sup_{s\in[t_1-\tau,t_1]} v(s) < \ell w_K(t_1 - \tau), \tag{4.15}$$

as v and w_K are continuous and assume their maximum on the interval $[t_1 - \tau, t_1]$ and w_K is strictly decreasing. From (4.14), for small $\delta < 0$, it follows

$$\frac{v(t_1 + \delta) - v(t_1)}{\delta} > \frac{\ell w_K(t_1 + \delta) - \ell w_K(t_1)}{\delta},$$

which in turn implies

$$D_- v(t_1) \ge \ell w_K'(t_1).$$

On the other hand, conditions (4.12), (4.14) and (4.15) imply

$$D_- v(t_1) \le -\alpha\ v(t_1) + \beta \sup_{s\in[t_1-\tau,t_1]} v(s) \ < -\alpha \ell w_K(t_1) + \beta\ \ell w_K(t_1 - \tau) = \ell w_K'(t_1).$$

This is a contradiction and thus, the premise that $v(t) = \ell w_K(t)$ for some $t = t_1 \in (t_0, T)$ is false. Equation (4.13) now follows. Now letting $\ell \to 1$ it is possible to conclude that $v(t) \le w_K(t)$; finally, since T is arbitrary, (4.11) follows. □

4.2.2 Conditions for stability

Consider the initial value problem (4.3). Sometimes it may be possible to obtain stability conditions by constructing of Lyapunov functionals. An example can be found in [5], where the authors obtained conditions of stability for the mathematical model of the

spread of infection disease by using a procedure of Lyapunov functionals construction. We want to propose stability conditions without the construction of Lyapunov functionals, but by comparison of Volterra integral equations, establishing the mean square stability of a stochastic integro-differential equation by comparison with a deterministic Volterra differential equation for the mean-square process associated with equation (4.3).

We will construct a comparison theorem to establish the asymptotic stability for the system (4.3). It could be regarded like an extension of the work developed by Baker and Buckwar for SDDEs with discrete delay [46].

Theorem 4.2.4. *Assume (a) conditions C_0, C_1, C_2 hold true and that $X(t) \equiv X(t; t_0, \phi)$ is a solution of equation (4.3) where $\tau \geq 0$. Assume (b) that there exists a function $V(t,x) \in C^{1,2}(J \times \mathbb{R}^d, \mathbb{R}_+)$ for which there exist positive constants c_1, c_2, such that*

$$c_1|x|^2 \leq V(t,x) \;\leq\; c_2|x|^2, \tag{4.16}$$

when $t \geq t_0 - \tau$ and $x \in \mathbb{R}^d$. Finally, suppose (c) that, for some values $0 \leq \beta < \alpha$,

$$D^+\mathbb{E}\big(V(t, X(t))\big) \leq -\alpha\mathbb{E}\big(V(t, X(t))\big) + \beta\mathbb{E}\big(V(t-\tau, X(t-\tau))\big), \tag{4.17}$$

when $t \geq t_0$. Then

$$\mathbb{E}(|X(t; t_0, \phi)|^2) \leq \frac{c_2}{c_1}\mathbb{E}(\|\phi\|^2)\ \exp(-\nu^+(t - t_0)). \tag{4.18}$$

with $\nu^+ \in (0, \alpha - \beta]$ the positive zero of $\Omega(\nu; \alpha, \beta, \tau)$ in (4.6); the trivial solution of equation (4.3) is exponentially mean-square stable.

Proof. The Dini derivative $D^+\mathbb{E}\big(V(t, X(t))\big)$ in (4.17) is $D^+v(t)$ where

$$v(t) := \mathbb{E}(V(t, X(t))) \equiv \mathbb{E}(V(t, X(t; t_0, \phi))).$$

Due to Condition C_1 and the continuity of X and V (cf., *e.g.*, [23, p. 172]) we see that $v(t)$ exists for $t \geq t_0 - \tau$ and is continuous (and non-negative); it is therefore Dini-differentiable for $t \in [t_0 - \tau, \infty)$. Equation (4.17) yields, expressed in terms of $v(t)$,

$$D^+v(t) \;\leq\; -\alpha v(t) + \beta \sup_{s\in[0,1]} v(t - s\tau), \quad t \geq t_0,$$

and we obtain from Theorem 4.2.3 the exponentially decreasing bound on $v(t)$:

$$v(t) \leq \big\{\sup_{s\in J} v(s)\big\}\ \exp\{-\nu^+(t - t_0)\} \quad \text{for } t_0 \leq t < \infty. \tag{4.19}$$

However, by (4.16),

$$\sup_{s\in J} v(s) \equiv \sup_{s\in J} \mathbb{E}(V(s,\phi(s))) \leq c_2 \sup_{s\in J} \mathbb{E}(|\phi(s)|^2) \leq c_2 \mathbb{E}(|\phi\|^2) \tag{4.20}$$

and

$$\mathbb{E}(|X(t)|^2) \ \leq \ \frac{1}{c_1} v(t), \tag{4.21}$$

for $c_1 = 0$ so that from (4.19) and (4.20) we obtain the desired result, which by Definition 3.2.1 implies the exponential mean-square stability of the trivial solution. □

Lemma 4.2.5. *Assume conditions C_0, C_1 and C_2 hold true. Let $V(t,x) \in C^{1,2}(J \times \mathbb{R}^d, \mathbb{R}_+)$ a function that satisfies Condition (4.16). Suppose that, when $t \geq 0$ and $X, Y \in \mathbb{R}^d$,*

$$\begin{aligned} V_t(t,X) + V_x(t,X)F(t,X,Y) + \frac{1}{2} trace[G^T(t,X,Y)V_{xx}(t,X)G(t,X,Y)] \\ \leq -\alpha V(t,X) + \beta V(t-\tau,X), \quad (0 \leq \beta \leq \alpha). \end{aligned} \tag{4.22}$$

Then the trivial solution of equation (4.3) is exponentially mean-square stable.

Proof. Let $X(t)$ a solution of equation (4.3). Applying the Itô formula in integral form, we obtain for $t \geq t_0$

$$\begin{aligned} &V(t+\delta, X(t+\delta)) - V(t, X(t)) \\ &\quad = \int_t^{t+\delta} V_t(s, X(s))ds + \int_t^{t+\delta} V_x(s, X(s))F(s, X(s), Y(s))ds + \\ &\quad \frac{1}{2}\int_t^{t+\delta} trace[G^T(s, X(s), Y(s))V_{xx}(s, X(s))G(s, X(s), Y(s))ds] + \\ &\quad \int_t^{t+\delta} V_x(s, X(s))G(s, X(s), Y(s))dW(s). \end{aligned}$$

Since $\mathbb{E}\left(\int_t^{t+\delta} V_x(s, X(s))G(s, X(s), Y(s))dW(s)\right) = 0$, taking expectations on both sides of the equality and applying the assumption (4.22) yields

$$\begin{aligned} &\mathbb{E}(V(t+\delta, X(t+\delta))) - \mathbb{E}(V(t, X(t))) \\ &\quad \leq \int_t^{t+\delta} \left(-\alpha \mathbb{E}(V(s, X(s))) + \beta \mathbb{E}(V(s-\tau, X(s)))\right) ds. \end{aligned}$$

Since the Dini D^+ is

$$D^+\mathbb{E}(V(t, X(t))) := \limsup_{\delta \to 0} \frac{\mathbb{E}(V(t+\delta, X(t+\delta))) - \mathbb{E}(V(t, X(t)))}{\delta},$$

the preceding result leads directly to

$$D^+\mathbb{E}(V(s,X(s))) \leq -\alpha\mathbb{E}(V(s,X(s))) + \beta\mathbb{E}(V(s-\tau,X(s)))$$

for $t \geq t_0$. By applying Theorem 4.2.4, the result follows. □

Theorem 4.2.6. *Assume there exists $k > 0$ such that*

$$X^T F(t,X,0) \leq -k|X|^2 \quad \textit{for all} \quad (t,X) \in [0,\infty) \times \mathbb{R}^d. \tag{4.23}$$

Assume also that there are nonnegative numbers $\alpha_1, \beta_0, \beta_1$ such that

$$|F(t,X,0) - F(t,X,Y)| \leq \alpha_1|Y| \tag{4.24}$$

and

$$|G(t,X,Y)|^2 \leq \beta_0|X|^2 + \beta_1|Y|^2 \tag{4.25}$$

for all $t \geq 0$ and $X, Y \in \mathbb{R}^d$. If the condition

$$k > \alpha_1 + \frac{1}{2}(\beta_0 + \beta_1) \tag{4.26}$$

is satisfied, then the trivial solution of equation (4.3) is exponentially mean-square stable.

Proof. Let $V(t,X) = |X|^2$. We need to establish an inequality of the form (4.22). Using the elementary inequality

$$|XY| \leq \frac{1}{2}(X^2 + Y^2), \quad \text{for} \quad X, Y \in \mathbb{R}^d.$$

and the conditions (4.23), (4.24) and (4.25), we obtain, for all $X, Y \in \mathbb{R}^d$,

$$\begin{aligned}
V_t(t,X) + V_x(t,X)F(t,X,Y) + \frac{1}{2}trace[G^T(t,X,Y)V_{xx}(t,X)G(t,X,Y)] \\
&= 2X^T F(t,X,0) + 2X^T\{F(t,X,Y) - F(t,X,0)\} + |G(t,X,Y)|^2 \\
&\leq -2k|X|^2 + 2X^T\alpha_1|Y| + \beta_0|X|^2 + \beta_1|Y|^2. \\
&\leq -2k|X|^2 + \alpha_1|X|^2 + \alpha_1|Y|^2 + \beta_0|X|^2 + \beta_1|Y|^2. \\
&\leq -(2k - \alpha_1 - \beta_0)|X|^2 + (\alpha_1 + \beta_1)|Y|^2 \\
&= -\alpha V(t,X) + \beta V(t-\tau,Y).
\end{aligned}$$

with $\tau > 0$ and $\alpha = 2k - \alpha_1 - \beta_0$ and $\beta = \alpha_1 + \beta_1$.
By virtue of (4.26), $\alpha > 0$ and $0 \leq \beta \leq \alpha$. The conclusion follows immediately from the Lemma 4.2.5 and the proof is complete. □

4.3 Stability in the first approximation

We now consider a nonlinear system

$$dX(t) = F(t, X_t)\, dt + G(t, X_t)\, dW(t), \quad t \geq t_0, \tag{4.27a}$$

$$X(t) = \phi(t) \quad t \in [t_0 - \tau, t_0], \tag{4.27b}$$

and a corresponding linear system of first-approximation

$$dX(t) = \tilde{F}(t, X_t)\, dt + \tilde{G}(t, X_t)\, dW(t), \quad t \geq t_0, \tag{4.28a}$$

$$X(t) = \phi(t) \quad t \in [t_0 - \tau, t_0], \tag{4.28b}$$

where $\bar{F}$ and $\bar{G}$ are linear in X_t. For $\tau > 0$ let $J := [-\tau, 0]$, we recall that $X_t(s) := X(t+s)$ for $s \in J$ denotes the history functional for X.

The stochastic delay differential equation (4.3) with distributed delay memory is a special case of (4.27). The initial function ϕ is a $\mathcal{F}_{t_0}-$ measurable $C(J; \mathbb{R})$-valued random variable, independent of $W(t)$ and with $\mathbb{E}\|\phi(t)\|^2 < \infty$.

We will denote a solution of equation (4.27), starting at t_0 and with initial function ϕ by $X(t; t_0, \phi)$. Assume that there exists a unique solution $X(t; t_0, \phi)$ of (4.27), corresponding to the initial set (t_0, ϕ).

In deterministic stability analysis for solutions of delay differential equations, one often utilizes a condition on the total derivative (suitably interpreted) of some *Lyapunov function* or *Lyapunov functional* along the solution trajectory. The approach followed here is an adaptation of the deterministic approach; one takes the Dini derivative of the expectation of $V(t, X(t))$ "along" $X(t)$. In this section we shall prove results concerning the mean square stability via a combination of comparison and Lyapunov function techniques, either regaining or extending Mao's results. Mao is essentially also using Dini-derivatives. In the next section we prove a general theorem for Lyapunov functionals, regaining Kolmanovskii and Nosov's result. The latter have used an integrated version of Dini-derivatives, and have then used $V(t, x) = |x|^2$ as a Lyapunov functional, making use of its differentiability and the Itô-formula. Hasminski proved $\mathbb{E}V(t, X(t))$ is differentiable (where $X(t)$ is a solution of an SODE), even sufficiently differentiable to use the Itô-formula. For our purposes it is not practical to assume sufficient differentiability for the Itô-formula, as this will be too much to get in the first approximation results.

The goal in this section is to obtain conditions under which the stability of the zero solution of (4.27) with nonlinear coefficient functions F and G is implied by the exponential stability of the null-solution of (4.28) with linear coefficient functions $\widetilde{F}$ and $\widetilde{G}$, where the differences $|F-\widetilde{F}|$ and $|G-\widetilde{G}|$ are small in some sense. Results of this type are the basis for the linear stability theory for numerical methods. A similar result is obtained in [17], but with different methods. In [28] results on stability in the first approximation are obtained, where the first approximation is a deterministic equation. The approach developed in the deterministic theory (for functional differential equations, see [35, 36, 45]) uses a converse theorem to prove the desired result. The converse theorem states that the exponential stability of the null-solution of a linear differential equation implies the existence of a Lyapunov function/functional with certain properties.

4.3.1 General properties

If we want to investigate the stability of a solution $X^*(t;t_0,\phi) \not\equiv 0$, and $X(t)$ is some other solution, we can make the substitution

$$U(t) = X(t) - X^*(t) \tag{4.29}$$

and find

$$dU(t) = (F(t, X_t^* + U_t) - F(t, X_t^*))dt + (G(t, X_t^* + U_t) - G(t, X_t^*))dW(t). \tag{4.30}$$

Introducing

$$\begin{aligned} \bar{F}(t,\psi) &= F(t, X_t^* + \psi) - F(t, X_t^*) \\ \bar{G}(t,\psi) &= G(t, X_t^* + \psi) - G(t, X_t^*), \end{aligned}$$

we have $\bar{F}(t,0) = \bar{G}(t,0) = 0$, so that $U(t) \equiv 0$ is a solution of (4.30). Thus the question of stability of a solution $X^*(t)$ can be reformulated as a question of stability of the zero solution (or equilibrium position or trivial solution) $X(t) \equiv 0$. In the sequel we will assume that $F(t,0) = G(t,0) = 0$ holds and study the mean-square stability of the zero-solution of equation (4.27).

Theorem 4.3.1. *Assume that F and G in (4.27a) be Lipschitz in x. Let $X_1(t;t_0,\phi_1)$ and $X_2(t;t_0,\phi_2)$ be two solutions of (4.27) with initial functions ϕ_1 and ϕ_2, respectively. Then*

$$|X_1(t;t_0,\phi_1) - X_2(t;t_0,\phi_2)| \leq e^{ML^2t}\|\phi_1 - \phi_2\|_J \tag{4.31}$$

[16]

Theorem 4.3.2. *Assume that F and G in (4.27a) be linear in x. Let $X_1(t;t_0,\phi_1)$ and $X_2(t;t_0,\phi_2)$ be two solutions of (4.27) with initial functions ϕ_1 and ϕ_2, respectively. Then the inequality*

$$X_{1+2}(t;t_0,\phi_1+\phi_2) := \alpha_1 X_1(t;t_0,\phi_1) + \alpha_2 X_2(t;t_0,\phi_2) \tag{4.32}$$

holds true and it is also a solution of (4.27a) to the initial conditions $\alpha_1\phi_1 + \alpha_2\phi_2$ [23].

Lemma 4.3.3. *Let f be a Lipschitz-continuous function from $\mathbb{R}$ to $\mathbb{R}^+$, which satisfies*

$$\int_z^\infty f(t)\mathrm{d}t < \infty \quad \text{for some} \quad z \in \mathbb{R}. \tag{4.33}$$

Then f has a limit at infinity and $\lim_{t\to\infty} f(t) = 0$ [36].

4.3.2 Mean square stability theorems

In this section we prove our new mean-square stability theorems which will allow us to create the basis of an original first approximation theory for stochastic delay differential equations not previously existent in the literature.

Define for $s \in J$

$$\begin{aligned} &\psi_t(s) = X(t+s;t_0,\phi), && \text{for all } t \geq 0 \\ &V^*(t) = \mathbb{E}V[t,\psi_t(s)] = \mathbb{E}V[t,X(t+s;t_0,\phi)] && \text{for all } t \geq 0. \end{aligned}$$

Theorem 4.3.4. *Assume that $X(t) \equiv X(t;t_0,\phi)$ is a solution of equation (4.27). Let us suppose that there exists a continuous functional $V[t,\psi_t]$ defined for every $t \geq 0$ and $\psi_t : [t-\tau,t] \to \mathbb{R}^d$, where $\tau > 0$, continuous functions such that $\mathbb{E}\|\psi_t\|_J^2 < H$,fixed constant, with the following properties:*
there exists positive constants $c_1,\ c_2,\ c_3$ with

1.

$$c_1\ \mathbb{E}|\psi_t(0)|^2 \ \leq\ \mathbb{E}V[t,\psi_t(s)] \ \leq\ c_2\ \mathbb{E}\|\psi_t\|_J^2. \tag{4.34}$$

2.

$$\limsup_{h\to 0+} \frac{\mathbb{E}V[t+h, X(t+h+s;t,\psi_t)] - \mathbb{E}V[t,\psi_t]}{h} \le -c_3\ \mathbb{E}\|\psi_t\|_J^2. \tag{4.35}$$

where $s \in J$.

Then the trivial solution of (4.27) *is asymptotically mean-square stable.*

Proof. For $\epsilon > 0$ take a $\delta(\epsilon) = \frac{c_1}{c_2}\epsilon$ and let $\mathbb{E}\|\phi\|_J^2 < \delta(\epsilon)$.
We have, if $\mathbb{E}\|\phi\|_J^2 = 0$

$$\limsup_{h\to 0+} \frac{V^*(t+h) - V^*(t)}{h} = \limsup_{h\to 0+} \frac{\mathbb{E}V[t+h, \psi_{t+h}(s)] - \mathbb{E}V[t,\psi_t(s)]}{h}$$

$$= \limsup_{h\to 0+} \frac{\mathbb{E}V[t+h, X(t+h+s;t_0,\phi)] - \mathbb{E}V[t,\psi_t(s)]}{h}$$

$$= \limsup_{h\to 0+} \frac{\mathbb{E}V[t+h, X(t+h+s;t,\psi_t(s))] - \mathbb{E}V[t,\psi_t(s))]}{h}$$

$$\le -c_3\mathbb{E}\|\psi_t\|_J^2 < -c_3 H < \quad 0.$$

From

$$\limsup_{h\to 0+} \frac{V^*(t+h) - V^*(t)}{h} \ < 0$$

it follows that $V^*(t)$ is monotone-decreasing, hence

$$V^*(t) \ \le \ V^*(t_0) \ = \ \mathbb{E}V[t_0,\psi_{t_0}]$$

$$\le \ c_2\ \mathbb{E}\|\psi_{t_0}\|_J^2 = c_2\mathbb{E}\|\phi\|_J^2 \le c_2\delta(\epsilon).$$

From (4.34) it follows

$$c_1\mathbb{E}|X(t;t_0,\phi)|^2 = c_1\ \mathbb{E}|\psi_t(0)|^2 \le V^*(t) \le c_2\ \delta(\epsilon),$$

and hence

$$\mathbb{E}|X(t;t_0,\phi)|^2 \le \frac{c_2}{c_1}\delta(\epsilon) = \epsilon$$

for $t \ge t_0$. Thus we have obtained the mean-square stability.
From (4.34) we have

$$c_1\mathbb{E}|X(t;t_0,\phi)|^2 = c_1\mathbb{E}|\psi_t(0)|^2 \le c_2\ \mathbb{E}\|\psi_t\|_J^2 < c_2 H$$

Applying the Itô formula, we conclude that $\mathbb{E}|X(t;t_0,\phi)|^2$ as a function of t satisfies the Lipschitz condition and

$$\int_{t_0}^{\infty} \mathbb{E}|X(t;t_0,\phi)|^2 dt < \infty.$$

In virtue of the Lemma 4.3.3, the proof is complete. □

Now we are going to prove a converse theorem which will serve to prove a stability theorem by first approximation.

Theorem 4.3.5. *If the trivial solution of the system (4.28) is exponentially mean-square stable,* i.e.*, the following inequality is satisfied*

$$\mathbb{E}|X(t;t_0,\phi)|^2 \leq A\mathbb{E}\|\phi\|_J^2 \ \exp(-\alpha(t-t_0)) \tag{4.36}$$

in the region

$$\mathbb{E}\|\phi\|_J^2 < H_0 = \frac{H}{A}, \tag{4.37}$$

then there exists a continuous functional $V[t,\psi_t]$, defined for every $t \geq 0$ and continuous functions $\psi_t : [t-\tau, t] \to \mathbb{R}^d$, $\tau > 0$, with the following properties:

1. $$c_1 \ \mathbb{E}\|\psi_t\|_J^2 \ \leq \ \mathbb{E}V[t,\psi_t(s)] \ \leq \ c_2 \ \mathbb{E}\|\psi_t\|_J^2. \tag{4.38}$$

2. $$\limsup_{h\to 0+} \frac{\mathbb{E}V[t+h, X(t+h+s;t,\psi_t)] - \mathbb{E}V[t,\psi_t]}{h} \leq -c_3 \ \mathbb{E}\|\psi_t\|_J^2. \tag{4.39}$$

3. $$\mathbb{E}|V[t,\psi_{t_1}] - V[t,\psi_{t_2}]| \leq c_2 \ \mathbb{E}(\sup_{s\in J}|\psi_{t_1}(s) - \psi_{t_2}(s)|^2) \tag{4.40}$$

where c_1, c_2, c_3 are positive constants.

Before to prove this result, we establish the following estimate we will need in the proof of this theorem.

Lemma 4.3.6. *Suppose the hypothesis of theorem 4.3.5 are satisfied. Then we have*

$$\mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \leq C\mathbb{E}\|\psi_t\|_J^2 \tag{4.41}$$

where $\psi_t(s) = X(t+s;t_0,\phi)$, for all $t \geq 0, s \in J$ and C is a constant given by

$$C = \max_{s\in J}\left(A\exp(-\alpha s)\left(\frac{\exp(\alpha)}{\exp(\alpha)-1} + \frac{(5C_1)\exp(-\alpha s)}{\alpha}\right)\right)$$

Proof. We have from (4.36) that for all $\sigma \geq 0, s \in J$

$$\mathbb{E}|X(t+\sigma+s;t,\psi_t)|^2 \leq A \ \mathbb{E}\|\psi_t\|_J^2 \ \exp(-\alpha(\sigma+s)). \tag{4.42}$$

We deduce from (4.42) that

$$
\begin{aligned}
&\mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \\
\leq\ & \mathbb{E}\sum_0^\infty \sup_{i<\sigma<i+1}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \quad = \quad \sum_{i=0}^\infty \mathbb{E}\sup_{i<\sigma<i+1}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \\
=\ & \sum_{i=0}^\infty \mathbb{E}\Bigg(\sup_{i<\sigma<i+1}\Big\| X(t+i+s;t,\psi_t) \\
&+ \int_i^\sigma \tilde{F}(u,X(t+u+s;t,\psi_t))du + \int_i^\sigma \tilde{G}(u,X(t+u+s;t,\psi_t))dW(u)\ \Big\|_J^2\Bigg) \\
\leq\ & \sum_{i=0}^\infty 3^2\mathbb{E}\Bigg(\sup_{i<\sigma<i+1}\|X(t+i+s;t,\psi_t)\|^2 \\
&+ \sup_{i<\sigma<i+1}\left\|\int_i^\sigma \tilde{F}(u,X(t+u+s;t,\psi_t))du\ \right\|^2 \\
&+ \sup_{i<\sigma<i+1}\left\|\int_i^\sigma \tilde{G}(u,X(t+u+s;t,\psi_t))dW(u)\ \right\|^2\Bigg) \\
\leq\ & \sum_{i=0}^\infty 3^2\Bigg(\mathbb{E}|X(t+i+s;t,\psi_t)|^2 + \mathbb{E}\left\|\int_i^{i+1}\tilde{F}(u,X(t+u+s;t,\psi_t))du\right\|^2 \\
&+ \mathbb{E}\sup_{i<\sigma<i+1}\left\|\int_i^\sigma \tilde{G}(u,X(t+u+s;t,\psi_t))dW(u)\right\|^2\Bigg) \\
\leq\ & \sum_{i=0}^\infty 3^2\Bigg(\mathbb{E}|X(t+i+s;t,\psi_t)|^2 + \mathbb{E}\int_i^{i+1}|\tilde{F}(u,X(t+u+s;t,\psi_t))|^2du \\
&+ 4\mathbb{E}\int_i^{i+1}|\tilde{G}(u,X(t+u+s;t,\psi_t))|^2du|\Bigg) \\
\leq\ & \sum_{i=0}^\infty 3^2\Bigg(\mathbb{E}|X(t+i+s;t,\psi_t)|^2 \\
&+ C_1\mathbb{E}\int_i^{i+1}|X(t+u+s;t,\psi_t)|^2du + 4C_1\mathbb{E}\int_i^{i+1}|X(t+u+s;t,\psi_t)|^2du|\Bigg) \\
\leq\ & \sum_{i=0}^\infty 3^2A\mathbb{E}\|\psi_t\|_J^2(\exp(-\alpha(i+s)) + (5C_1)\|\psi_t\|_J^2\int_i^{i+1}\exp(-\alpha(u+s))du) \\
\leq\ & C\mathbb{E}\|\psi_t\|_J^2
\end{aligned}
$$

where $C = \max_{s\in J}\Big(A\exp(-\alpha s)(\frac{\exp(\alpha)}{\exp(\alpha)-1} + \frac{(5C_1)\exp(-\alpha s)}{\alpha})\Big)$, C_1 is the constant for the linear growth condition of the drift and diffusion functions. In the fourth inequality we used Hölder and Burkholder-Davis-Gundy's inequalities [23]. The lemma is proved.

□

Proof. (Proof of Theorem 4.3.5)
We define the functional

$$V[t,\psi_t] = \int_0^\infty \|X(t+u+s;t,\psi_t)\|_J^2\ du + \sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \tag{4.43}$$

where $\psi_t(s) = X(t+s;t_0,\phi)$, for all $t \geq 0, s \in J$, and show that it has the desired properties.

1. The left inequality of (4.38) (with $c_1 = 1$) follows obviously from the definition 4.43

$$\mathbb{E}V[t,\psi_t] \geq \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \geq \mathbb{E}\|\psi_t\|_J^2$$

We deduce from lemma 4.3.6 that

$$\begin{aligned}
\mathbb{E}V[t,\psi_t] &\leq \int_0^\infty A\ \mathbb{E}\|\psi_t\|_J^2\ \exp(-\alpha(u+s))\ du + \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_t)\|_J^2 \\
&\leq A\ \mathbb{E}\|\psi_t\|_J^2\exp(-\alpha s)\int_0^\infty \exp(-\alpha u)\ du + C\mathbb{E}\|\psi_t\|_J^2 \\
&= A\ \mathbb{E}\|\psi_t\|_J^2\exp(-\alpha s)(\frac{1}{\alpha}) + C\mathbb{E}\|\psi_t\|_J^2 \\
&\leq c_2\mathbb{E}\|\psi_t\|^2
\end{aligned}$$

where $c_2 = \max_{s\in J}\big(A\exp(-\alpha s)(\frac{1}{\alpha}) + C\big)$.

2. We have

$$\begin{aligned}
\mathbb{E}V[t,X(t+s;t,\psi_t)] &= \mathbb{E}\int_0^\infty \|X(t+u+s;t,X(t+s;t,\psi_t))\|_J^2\ du \\
&\quad + \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,X(t+s;t,\psi_t))\|_J^2 \\
&= \mathbb{E}\int_0^\infty \|X(t+u+s;t,X(t+s;t_0,\phi))\|_J^2\ du \\
&\quad + \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,X(t+s;t_0,\phi))\|_J^2 \\
&= \mathbb{E}\int_t^\infty \|X(u+s;t_0,\phi)\|_J^2 du + \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t_0,\phi)\|_J^2
\end{aligned}$$

It is possible to prove that $\mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t_0,\phi)\|_J^2$ is a monotone-decreasing function (*e.g.*, see [45], pag. 344, for a hint).
Further,

$$\limsup_{h\to 0+}\frac{\mathbb{E}V[t+h,X(t+h+s;t,\psi_t(s))]-\mathbb{E}V[t,\psi_t(s)]}{h}$$

$$\leq \frac{d}{dt}\mathbb{E}\int_t^\infty \|X(u+s;t_0,\phi)\|_J^2 du = -\mathbb{E}\|X(t+s;t_0,\phi)\|_J^2 = -\mathbb{E}\|\psi_t\|_J^2$$

The statement is thus proved for $c_3 = 1$.

3. By applying lemma 4.3.6 and by using the elementary inequalities

$$|a+b|\leq |a|+|b| \qquad |a|-|b|\leq |a-b|$$

$$|sup(A)-sup(B)|\leq |sup(A)-inf(B)| = |sup(A-B)|$$

and the triangle inequality, we obtain

$$\begin{aligned}
&|\mathbb{E}V[t,\psi_{t_1}]-\mathbb{E}V[t,\psi_{t_2}]|\\
&= \Big|\int_0^\infty \mathbb{E}\|X(t+u+s;t,\psi_{t_1})\|_J^2\ du + \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_{t_1})\|_J^2\\
&\quad -\int_0^\infty \mathbb{E}\|X(t+u+s;t,\psi_{t_2})\|_J^2\ du - \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_{t_2})\|_J^2\Big|\\
&\leq \int_0^\infty |\mathbb{E}\|X(t+u+s;t,\psi_{t_1})\|_J^2\ - \mathbb{E}\|X(t+u+s;t,\psi_{t_2})\|_J^2|du\\
&\quad +|\mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_{t_1})\|_J^2 - \mathbb{E}\sup_{\sigma>0}\|X(t+\sigma+s;t,\psi_{t_2})\|_J^2|\\
&\leq \int_0^\infty |A\ \mathbb{E}\ \exp(-\alpha(u+s)(\|\psi_{t_1}\|_J^2-\|\psi_{t_2}\|_J^2)|du + |C\mathbb{E}(\|\psi_{t_1}\|_J^2-\|\psi_{t_2}\|_J^2)|\\
&\leq c_2\mathbb{E}\|\psi_{t_1}-\psi_{t_2}\|.
\end{aligned}$$

The proof is complete. □

We assume that the following inequalities are satisfied

$$|F(t,X_t)-\tilde{F}(t,X_t)|+|G(t,X_t)-\tilde{G}(t,X_t)|\leq\gamma|X_t| \tag{4.44}$$

γ being sufficiently small for $\mathbb{E}\|\phi\|_J^2 < H$.

Lemma 4.3.7. *Assume that F and G in (4.27) be Lipschitz in X. Let $X(t;t_0,\phi_1)$ be the solution of (4.27) and $\tilde{X}(t;t_0,\phi_2)$ the solution of (4.28) with initial functions ϕ_1 and ϕ_2, respectively. Then*

$$|X(t;t_0,\phi_1)-\tilde{X}(t;t_0,\phi_2)|\leq (e^{L^{t-t_0}}-1)(|F-\tilde{F}|-|G-\tilde{G}|) \tag{4.45}$$

Theorem 4.3.8. *Let us consider the systems (4.28) and (4.27) with inequalities (4.44). If the trivial solution of the first-approximation linear system (4.28) is exponentially mean-square stable, the the trivial solution of system (4.27) is asymptotically mean-square stable.*

Proof. Let $V[t, \psi_t]$ be the functional defined for system (4.28) on the basis of Theorem 4.3.5. We evaluate the functional along solutions X of (4.27).

Define for $s \in J := [-\tau, 0]$

$$\begin{aligned} &\tilde{\psi}_t(s) = X(t+s; t_0, \psi_t), && \text{for all } t \geq 0 \\ &V^*(t) = \mathbb{E}V[t, \tilde{\psi}_t(s)] = \mathbb{E}V[t, X(t+s; t_0, \psi_t)] && \text{for all } t \geq 0. \end{aligned}$$

We want to prove that the conditions (4.34) and (4.35) of Theorem 4.3.4 are satisfied for the solution X of (4.27). Let $\tilde{X}$ be the solution of the linear system of (4.28) We evaluate

$$\limsup_{h \to 0+} \frac{V^*(t+h) - V^*(t)}{h} \tag{4.46}$$

in order to prove the condition (4.34). The condition (4.35) is given by Theorem 4.3.5. We have

$$\begin{aligned} & \limsup_{h \to 0+} \frac{V^*(t+h) - V^*(t)}{h} \\ = & \limsup_{h \to 0+} \frac{\mathbb{E}V[t, X(t+h+s; t_0, \phi)] - \mathbb{E}V[t, X(t+s; t_0, \phi)]}{h} \\ \leq & \limsup_{h \to 0+} \frac{\mathbb{E}V[t, \tilde{X}(t+h+s; t, \tilde{\psi}_t)] - \mathbb{E}V[t, X(t+s; t_0, \phi)]}{h} \\ & + \limsup_{h \to 0+} \frac{\mathbb{E}V[t, X(t+h+s; t_0, \phi)] - \mathbb{E}V[t, \tilde{X}(t+s; t, \tilde{\psi}_t)]}{h} \end{aligned} \tag{4.47}$$

(4.48)

By applying (4.39) on the first limit we obtain

$$\begin{aligned} & \limsup_{h \to 0+} \frac{\mathbb{E}V[t, \tilde{X}(t+h+s; t, \tilde{\psi}_t)] - \mathbb{E}V[t, X(t+s; t_0, \phi)]}{h} \\ = & \limsup_{h \to 0+} \frac{\mathbb{E}V[t, \tilde{X}(t+h+s; t, \tilde{\psi}_t)] - \mathbb{E}V[t, X(t+s; \tilde{\psi}_t)]}{h} \\ \leq & -c_3 \mathbb{E}\|\tilde{\psi}_t\| \end{aligned} \tag{4.49}$$

where c_3 is a positive constant. Setting $\psi_1 = X(t+h+s;t_0,\phi)$ and $\psi_2 = \tilde{X}(t+s;t,\tilde{\psi}_t)$ and according to property (4.40) we have that there exists c_2, a positive constant, such that

$$\begin{aligned} & \mathbb{E}V[t, X(t+h+s;t_0,\phi)] - \mathbb{E}V[t, \tilde{X}(t+s;t,\tilde{\psi}_t)] \\ = \; & \mathbb{E}V[t,\psi_1)] - \mathbb{E}V[t,\tilde{X}(t+s;t,\psi_2)] \\ \leq \; & c_2\mathbb{E}\|\psi_1 - \psi_2\| \end{aligned} \tag{4.50}$$

From (4.50), on the basis of the estimate (4.3.7) and the hypothesis (4.44) made with respect to the drift and diffusion coefficients, we obtain

$$\begin{aligned} & c_2\mathbb{E}\|X(t+h+s;t_0,\phi) - \tilde{X}(t+s;t,\tilde{\psi}_t)\| \\ \leq \; & c_2(\exp L(t-t_0)-1)\mathbb{E}|F(t+h,X(t+h+s;t_0,\phi)) - \tilde{F}(t+h,X(t+h+s;t_0,\phi))| \\ & + c_2(\exp L(t-t_0)-1)\mathbb{E}|G(t+h,X(t+h+s;t_0,\phi)) - \tilde{G}(t+h,X(t+h+s;t_0,\phi))| \\ \leq \; & c_2\gamma(e^{L(t-t_0)}-1)\mathbb{E}\|X(t+h+s;t_0,\phi)\| = 2c_2\gamma(e^{L(t-t_0)}-1)\mathbb{E}\|\tilde{\psi}_t\| \end{aligned} \tag{4.51}$$

Hence from (4.47), (4.49) and (4.51) we have

$$\begin{aligned} & \limsup_{h\to 0+} \frac{V^*(t+h)-V^*(t)}{h} \\ \leq \; & -c_3\mathbb{E}\|\tilde{\psi}_t\| + c_2\gamma(e^{L(t-t_0)}-1)\mathbb{E}\|\tilde{\psi}_t\| \\ = \; & (-c_3 + c_2\gamma(e^{L(t-t_0)}-1))\mathbb{E}\|\tilde{\psi}_t\| \end{aligned}$$

For $\gamma \leq c_3(1/c_2e^{L(t-t_0)})$ we obtain (4.35) of Theorem 4.3.4 and then the theorem is proved.

□

We will give an application of the Theorem 4.2.6 in the next section.

5

Application to an immune response model

In this chapter we formulate a new stochastic model for the human immune response and we apply our stability theorems obtained in the last chapter to study the stochastic stability properties of equilibria of the stochastic immune model. We successfully obtain conditions of stability in terms of thresholds of the parameter values and the amplitude of noise, which are proved in the last theorem of this chapter.

5.1 Modelling an immune system

We consider a mathematical model describing the human immune response system. The immune system is a complex integrated network of chemical mediators and cells developed in the course of evolution to protect the body against the presence of infectious organisms, usually referred to pathogens. In general four types of pathogens cause disease in humans: bacteria, fungi, viruses and protozoa. An important aspect of any pathogen system is the mechanism by which it is able to invade a host cell. Pathogens can communicate with human cells by physical interactions with several human proteins on the surface of the cell and within the interior of the cell. Through these interactions, the pathogen enters the host cell, manipulates important cellular processes, multiplies, and invades other cells [47]. Pathogens may replicate intra-cellularly (viruses and some bacteria and parasites) or extracellularly (most bacteria, fungi and parasites). Detection within the human body is complicated as pathogens can evolve rapidly, producing

adaptations that avoid the immune system and allow the pathogens to successfully infect their hosts.

The key feature of the immune system is the ability to distinguish between endogenous and exogenous structures which are not dangerous and may or must be preserved (*self*) and endogenous and exogenous structures which are harmful for the body and must be eliminated (*non-self*). Virtually every body cell carries distinctive molecules that identify it as self [48]. The body's immune defences do not normally attack tissues that carry a self marker. Rather, immune cells and other body cells coexist in a state known as self-tolerance. But when immune defenders encounter cells or organisms carrying molecules that say "foreign", start the immune alert to eliminate the intruders. Any substance capable of triggering an immune response is called an antigen (short for *anti*body *gene*rators). An antigen can be a virus, a bacterium, a fungus, or a parasite, or even a portion or product of one of these organisms. Tissues or cells from another individual, except an identical twin whose cells carry identical self-markers, also act as antigens; because the immune system recognizes transplanted tissues as foreign, it rejects them. The body will even reject nourishing proteins unless they are first broken down by the digestive system into their primary, non-antigenic building blocks. An antigen announces its foreignness by means of intricate and characteristic shapes called epitopes, which protrude from its surface. Most antigens, even the simplest microbes, carry several different kinds of epitopes on their surface; some may carry several hundred [49]. However, some epitopes will be more effective than others at stimulating an immune response. In abnormal situations, the immune system can wrongly identify self as nonself and execute a misdirected immune attack. The result can be a so-called autoimmune disease such as rheumatoid arthritis or systemic lupus erythematosus. In some people, an apparently harmless substance such as ragweed pollen or cat hair can provoke the immune system to set off the inappropriate and harmful response known as allergy; in these cases the antigens are known as allergens [50].

The key feature of the immune system is the ability to distinguish between endogenous and exogenous structures which are not dangerous and may or must be preserved (*self*) and endogenous and exogenous structures which are harmful for the body and must be eliminated (*non-self*). One class of non-self molecules are called *antigens* (short for *anti*body *gene*rators) The discrimination between self and non self, then necessary to protect the organism from invading pathogens and to eliminate modified or altered

cells (e.g. malignant cells), is mediated by specific cellular structures (Toll-like receptors , receptors of T lymphocytes, antibodies), which allow the recognition of antigens [51]. Depending on the different mechanism and receptors used for the immune recognition of antigens [52], the human immune response is usually divided into two components: *innate* (non specific) response and *adaptive* (specific) response.

5.1.1 Innate response

The Innate response is the first and evolutionarily older strategy defence of the human body to the presence of pathogens (bacteria, virus). The first line of defence against invading organism is provided by the anatomical barriers of the human body (i.e.skin, gastrointestinal tract, respiratory airways and lungs, eyes). When a pathogen breaches these barriers, the innate immune system provides an immediate but non-specific response, meaning this system responds to pathogens in a generic way and then allows the recognition of a limited repertoire of antigens.
The major functions of the innate immune system include:

- Produce chemical factors (e.g. specialized chemical mediators *called cytokines*), to recruit immune cells, such as phagocytes, mast cells, eosinophils, basophils and natural killer cells. to sites of infection.
- Activate the complement system, i.e. a biochemical cascade that 'complements' the ability of antibodies to identify bacteria and clear pathogens or mark them for destruction by other cells. cells or antibody complexes.
- The identification and removal of foreign substances present in organs, tissues, the blood and lymph, by specialized white blood cells.

The speed of recognition and defence response, which occurs on the order of minutes and hours, is thus due to the fact that the recognition mechanisms are equally on all components of non-specific immunity and are fully determined at the genetic level without any need for such epigenetic processes of maturation. The simplicity and speed that characterize this system are obtained through the price of not optimal effectiveness in the elimination of many pathogens and an inability to adapt to countermeasures developed by pathogenic micro-organisms. When the pathogens evade this first line of

defence of the body, then a more specific immune system is activated by the innate system through a process known as antigen presentation [53].

5.1.2 Adaptive response

The specific immunity includes the cellular and chemical mediators of a defensive response more powerful and focused. It is able to recognize virtually any antigen, but it is slower. occurring on the order of day or weeks. It is evolutionarily more recent and has been selected by evolution for its ability to dynamically adapt to the variability of environmental agents recognised as a threat to the organism. During the process of antigen presentation induced by the innate immunity, the specific immune system can distinguish between self and non-self and reacts against non-self. There is a high degree of specificity in its reactions. A response to a particular antigen is specific for that antigen or a few closely related antigens [48]. The adaptive immune system is mainly composed of cells of the lymphoid: T-series and B. B cells and T cells are derived from the same stem cells, and are indistinguishable from one another until after they are activated. However B cells (and T-cells) are produced by stem cells in the bone marrow. T-cells travel to and develop in the thymus, from which they derive their name.

- B cells play a large role in the extracellular immune response. The process of extracellular defence begins when a lymphocyte encounters a foreign agent through its specific receptor and starts to produce cell will be allocated in part to immunologic memory and in part of the plasma cells [47]. Plasma cells then produce antibodies that will bind to the outer body by blocking its active sites facilitating phagocytosis by macrophages.

- The intracellular immune response is carried out by cytotoxic T lymphocytes , which destroy a virus that has infected a cell. T cells through specific receptors bind to the complex self non-self exposed recognised by APC cells (*antigen presenting cells*) so that they can create holes in the cell wall by the action of an enzyme called perforin, secreted by them. This leads to cell lysis.

When B cells and T cells are activated some will become *memory cells* [54]. These memory cells form a database of effective B and T lymphocytes and upon interaction with a previously encountered antigen, the appropriate memory cells are selected and activated. In this way the second exposures to an antigen produce a stronger and faster immune response. This is "adaptive" because the body's immune system prepares itself for future challenges. Immunological memory can either be in the form of passive short-term memory (e.g. the fetus borrows memory cells or antibodies from the mother or the transfer of immunity via antibody-rich serum) or active long-term memory (*e.g.*, natural immunity acquired by infection followed by B cells and T cells activation, artificial immunity acquired by vaccines) [55].

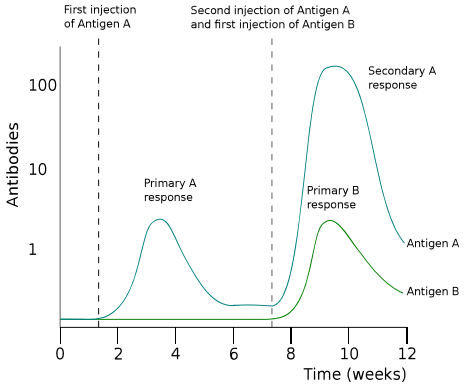


Figure 5.1: Memory of adaptive immune response.

5.1.3 Timing and delays in immune system

It is important to notice that each part of the immune system has a time delay in their development, which is important to determine the success or the failure in the act of removing the pathogen infection. Once recognition occurs, the innate immune system is activated and works with very rapid kinetics, on the orders of minutes to hours.
The signals induced upon recognition by the innate immune system, in turn, stimulate and orient the adaptive immune response. Thus, the adaptive immune system responds to pathogens only after they have been recognized by the innate system [56]. It takes at least 3 to 5 days for sufficient numbers of adaptive immune cells to be produced. Another delay beyond the recognition and expansion phase occurs due to activation and differentiation phases because in order to complete these phases cells have to circulate

and traffic from the lymphatic system through the blood to the site of infection [57]. This process takes at least few days [49].

Taking account of these time delays, in 2007 Beretta, Carletti, Marino and Kirschner in [58] developed a mathematical model describing the dynamics of the Human Immune Response. It consists of a Delay Differential Equations (DDEs) system of five equations. The two delays relative to the innate and adaptive responses are described by distributed delay functions, with different kernels. They studied the stability of two equilibria of this mathematical model. We are interested to analyse the robustness of these equilibria using a stochastic version of the deterministic model.
The chapter is organized as follows. In Section 5.2 we describe the deterministic model presented in [18] and in Section 5.2.1 we describe the stability properties of the equilibria of this deterministic model found in [18, 58]. In Section 5.3 we present our stochastic model for the immune response. We perturb the deterministic model by multiplicative noise proportional to the distance of variables to the equilibrium. Then we investigate the stability of the equilibrium of this stochastic system by applying the theoretical results proved in Chapter 4. For an interested reader to a multidisciplinary approach to the formulation of quantitatively correct mathematical models of the immune system, we refer to [59].

5.2 Deterministic immune response model

In order to model the two-fold human immune system, it is important to notice that the time plays a crucial role. The immune system is characterized by a natural temporal kinetic. The innate response, which is the first line of defence activated to attempt to clear any invasion by microbes, develops with very rapid kinetics, on the orders of minutes to hours.
If the innate immunity fails, the adaptive response follows and it occurs on the order of days to weeks. Considering the two ways of immune response which run on two time scales, Beretta *et al.* in [58] modelled that incorporating mathematical delays for both innate and adaptive immune response. They developed this model considering two distributed delays, for each of the immune responses and studying how each affected infection outcome. In 2007 Beretta, Kirshner and Marino [18] extended this model

introducing a term that accounts for direct killing of bacteria due to adaptive immunity. We are going to consider this system for our study.

The DDEs baseline model for the human immune response model consists of five variables: x_U are the uninfected target cells, x_I the infected cells, b the bacteria, i_R and a_R are the variables for innate and adaptive immunity. The model introduced by Beretta, Kirshner and Marino in [18] is governed by

$$\begin{aligned}
\frac{\mathrm{d}x_U(t)}{\mathrm{d}t} &= s_U - \alpha_1 x_U(t) b(t) - \mu_{x_U} x_U(t) \\
\frac{\mathrm{d}x_I(t)}{\mathrm{d}t} &= \alpha_1 x_U(t) b(t) - \alpha_2 x_I(t) a_R(t) - \mu_{x_I} x_I(t) \\
\frac{\mathrm{d}b(t)}{\mathrm{d}t} &= \alpha_{20} b(t) \left(1 - \frac{b(t)}{\sigma}\right) - \alpha_3 b(t) i_R(t) - \alpha_4 b(t) a_R(t) \\
\frac{\mathrm{d}i_R(t)}{\mathrm{d}t} &= s_{i_R} + \int_{-\tau_1}^{0} w_1(\theta) b(t+\theta) \mathrm{d}\theta - \mu_{i_R} i_R(t) \\
\frac{\mathrm{d}a_R(t)}{\mathrm{d}t} &= s_{a_R} + \int_{-\tau_2}^{0} w_2(\theta) b(t+\theta) \mathrm{d}\theta - \mu_{a_R} a_R(t).
\end{aligned} \tag{5.1}$$

In the first equation s_U and μ_{x_U} are respectively the natural turnover and the half-life of uninfected target cells x_U. Of these, the number which can become infected is given by the mass-action term $\alpha_1 x_U b$. The second equation describes the evolution of the infected cells x_I, which can be cleared by the adaptive response ,the number of which is given by the mass-action term $\alpha_2 x_I a_R$, or die with half-life term μ_{x_I}. The third equation is related to the bacteria population, which has a net proliferation term $\alpha_{20} b(t) \left(1 - \frac{b(t)}{\sigma}\right)$ and can be cleared by innate immunity given by the mass-action term $\alpha_3 b(t) i_R(t)$ and adaptive immunity given by the mass-action term $\alpha_4 b(t) a_R(t)$. The last two equations describe the evolution of innate i_R and adaptive a_R responses and include the two delays. Both innate and adaptive cells have a source term denoted s_{i_R} and s_{a_R}, respectively, and an half-life term denoted by μ_{i_R} and μ_{a_R}, respectively. The two delays of the immune response are denoted by τ_1 for the innate part (minutes to hours) and by τ_2 for the adaptive part (days to weeks). The kernel functions $w_i(s), (i = 1, 2)$ weights the past values of the bacteria load $b(s)$. They could be of two different types: exponential or uniform. It is assumed that all parameters are positive constants and they are evaluated in quite large ranges, suggested in several published data. We have collected the parameters and their ranges in Table 5.1, except for the half-life coefficients, which have well defined values (for references of the data see [58] and [18]).

Name	Definition	Range	Units
μ_{x_U}	Half-life of x_U	0.011	$1/day$
α_1	Rate of infection of x_U	$[10^{-5}, 1]$	$b(t)^{-1}/day$
α_2	Rate of killing of x_I due to a_R	$[10^{-5}, 1]$	$a_R(t)^{-1}/day$
μ_{x_I}	Half-life of x_I	0.011	$1/day$
α_{20}	Growth rate of b	$[10^{-5}, 1]$	$1/day$
σ	Max # Threshold of Bacteria	$[10^4, 1e^6]$	$b(t)$
α_3	Rate of killing of b due to i_R	$[10^{-5}, 1]$	$i_R(t)^{-1}/day$
α_4	Rate of killing of b due to a_R	$[10^{-5}, 1]$	$a_R(t)^{-1}/day$
μ_{i_R}	Half-life of innate immunity cells	0.11	$1/day$
μ_{a_R}	Half-life of adaptive immunity cells	0.33	$1/day$
τ_1	Delay of innate immunity	[.1, 10]	day
τ_2	Delay of adaptive immunity	[5, 40]	day

Table 5.1: Parameter values for the model of the human immune response.

Further, Table 5.2 contains the range for the initial data.

Name	Range
$x_U(0)$	10^4 – 10^5
$x_I(0)$	0
$b(0)$	20
$i_R(0)$	10^3 – 10^4
$a_R(0)$	10^2 – 10^3

Table 5.2: Initial data for the model of the human immune response (cells or bacteria per cm^3 of tissue) described in equation (5.1).

In order to well define the integrals in the last two equations of system (5.1), we consider the following initial conditions.

$$\begin{cases} x_I(t) \equiv 0 & \text{for} \quad t \in [-\tau_2, 0] \\ b(t) \equiv b(0) & \text{for} \quad t \in [-\tau_2, 0] \\ i_R(t) \equiv i_R(0) & \text{for} \quad t \in [-\tau_1, 0] \\ a_R(t) \equiv a_R(0) & \text{for} \quad t \in [-\tau_2, 0] \end{cases} \tag{5.2}$$

Given the initial conditions and half-life terms, the values of source terms are deter-

mined by the following conditions

$$s_U \equiv \mu_{x_U} x_U(0), \quad s_{i_R} \equiv \mu_{i_R} i_R(0), \quad s_{a_R} \equiv \mu_{a_R} a_R(0). \tag{5.3}$$

As unit measurement we used the same choice taken by Beretta *et al.* in their papers, *i.e.*, number of cells per cm^3 of tissue. Modelling the complex immune system of innate and adaptive responses is important in understanding disease progression and can be useful to develop more efficient therapies and vaccines. It is decisive to understand how timing and delays in innate and adaptive responses can affect host immunity versus bacterial infection. In the next Section we describe the local stability properties of the equilibria of the model system (5.1) and their dependence on the two delays.

5.2.1 Stability of equilibria for the deterministic model

By basic computations it is possible to find two non-negative equilibria for the system (5.1): a boundary equilibrium point, corresponding to the healthy or uninfected state, and an interior equilibrium, which corresponds to the infection setting.

- Boundary equilibrium $E_B = (x_U^*, 0, 0, i_R^*, a_R^*) = \left(\dfrac{s_U}{\mu_{x_U}},\ 0,\ 0,\ \dfrac{s_{i_R}}{\mu_{i_R}},\ \dfrac{s_{a_R}}{\mu_{a_R}} \right).$
- Positive equilibrium $E_P = (x_U^*, x_I^*, b^*, i_R^*, a_R^*)$
  for
  $$R_0 := \alpha_{20} - \alpha_3 \frac{s_{i_R}}{\mu_{i_R}} - \alpha_4 \frac{s_{a_R}}{\mu_{a_R}} > 0, \tag{5.4}$$

  where
  $$x_U^* = \frac{s_U}{\alpha_1 b^* + \mu_{x_U}}, \qquad x_I^* = \frac{\alpha_1 b^* x_U^*}{\alpha_2 a_R^* + \mu_{x_I}},$$
  $$b^* = \frac{\alpha_{20} - \alpha_3 \frac{s_{i_R}}{\mu_{i_R}} - \alpha_4 \frac{s_{a_R}}{\mu_{a_R}}}{\frac{\alpha_{20}}{\sigma} + \alpha_3 \frac{\Delta(\tau_1)}{\mu_{i_R}} + \alpha_4 \frac{\Delta(\tau_2)}{\mu_{a_R}}},$$
  $$i_R^* = \frac{s_{i_R} + \Delta(\tau_1) b^*}{\mu_{i_R}}, \qquad a_R^* = \frac{s_{a_R} + \Delta(\tau_2) b^*}{\mu_{a_R}},$$

  with the following notation
  $$\Delta(\tau_i) = \int_{-\tau_i}^{0} w_i(\theta) \mathrm{d}\theta, \qquad i = 1, 2.$$

We observe that:

- the equilibrium E_B exists on the boundary of the positive cone in $\mathbb{R}^5$ and the equilibrium E_P is in the interior of the positive cone in $\mathbb{R}^5$;
- if $R_0 = 0$, then E_P coincides with E_B, when $R_0 < 0$, there exists only the boundary equilibrium E_B.

After linearisation of the system (5.1) around any of the equilibria, we obtain the following system for $x(t) = (x_U, x_I, b, i_R, a_R)^T$

$$\frac{dx(t)}{dt} = Lx(t) + \int_{-h}^{0} K(\theta)x(t+\theta)d\theta.$$

where $L \in \mathrm{R}^{5\times 5}$ is the matrix

$$\mathbf{L} = \begin{pmatrix} -\alpha_1 b^* - \mu_{x_U} & 0 & -\alpha_1 x_U^* & 0 & 0 \\ \alpha_1 b^* & -\alpha_2 a_R^* - \mu_{x_I} & \alpha_1 x_U^* & 0 & -\alpha_2 x_I^* \\ 0 & 0 & \left(\alpha_{20} - \alpha_3 i_R^* - \frac{2\alpha_{20}}{\sigma} b^* - \alpha_4 a_R^*\right) & -\alpha_3 b^* & -\alpha_4 b^* \\ 0 & 0 & 0 & -\mu_{i_R} & 0 \\ 0 & 0 & 0 & 0 & -\mu_{a_R} \end{pmatrix}$$

and $K(\theta) : [-h, 0] \to \mathbb{R}^{5\times 5}$, $h = \max \tau_1, \tau_2$ is the matrix function

$$\mathbf{K} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \tilde{w}_1(\theta) & 0 & 0 \\ 0 & 0 & w_2(\theta) & 0 & 0 \end{pmatrix}$$

where $h = \max\{\tau_1, \tau_2\}$ (*i.e.*, $h = \tau_2$) and $\tilde{w}_1(\theta) = \begin{cases} w_1(\theta) & \text{in } [-\tau_1\,,\, 0] \\ 0 & \text{in } [-\tau_2\,,\, -\tau_1]\,. \end{cases}$

The associated characteristic equation is

$$\det\left(\lambda\mathbf{I} - \mathbf{L} - \int_{-h}^{0} \mathbf{K}(\theta)\, e^{\lambda\theta} d\theta\right) = \quad 0 \tag{5.5}$$

where $\mathbf{I} \in \mathbb{R}^{5\times 5}$ is the identity matrix and λ are the characteristic roots.
By defining

$$F_i(\lambda) := \int_{-\tau_i}^{0} w_i(\theta) e^{\lambda\theta} d\theta, \qquad i = 1, 2, \tag{5.6}$$

we get the following characteristic equation

$$\begin{array}{l}\left[\lambda+\left(\alpha_1 b^*+\mu_{x_U}\right)\right]\left[\lambda+\left(\alpha_2 a_R^*+\mu_{x_I}\right)\right]\cdot \\ \cdot\det\begin{pmatrix}\lambda-\left(\alpha_{20}-\alpha_3 i_R^*-\frac{2\alpha_{20}}{\sigma}b^*-\alpha_4 a_R^*\right) & \alpha_3 b^* & \alpha_4 b^* \\ -F_1(\lambda) & \lambda+\mu_{i_R} & 0 \\ -F_2(\lambda) & 0 & \lambda+\mu_{a_R}\end{pmatrix}=0.\end{array}$$

Then there are two negative characteristic roots

$$\lambda_1=-\left(\alpha_1 b^*+\mu_{x_U},\right)\qquad \lambda_2=-\left(\alpha_2 a_R^*+\mu_{x_I},\right) \tag{5.7}$$

and the other characteristic roots are solutions of

$$\det\begin{pmatrix}\lambda-\left(\alpha_{20}-\alpha_3 i_R^*-\frac{2\alpha_{20}}{\sigma}b^*-\alpha_4 a_R^*\right) & \alpha_3 b^* & alpha_4 b^* \\ -F_1(\lambda) & \lambda+\mu_{i_R} & 0 \\ -F_2(\lambda) & 0 & \lambda+\mu_{a_R}\end{pmatrix}=0. \tag{5.8}$$

The study of the characteristic equation (5.5) is reduced to the study of equation (5.8) and the characteristic roots in (5.8) are dependent on both delays τ_1 and τ_2.

The following result concerns the stability of the boundary equilibrium E_B established for all parameters values in [18].

Theorem 5.2.1. *The boundary equilibrium E_B is:*

1. *asymptotically stable if*

$$\alpha_{20}-\alpha_3\frac{s_{i_R}}{\mu_{i_R}}-\alpha_4\frac{s_{a_R}}{\mu_{a_R}}<0;$$

2. *linearly neutrally stable if*

$$\alpha_{20}-\alpha_3\frac{s_{i_R}}{\mu_{i_R}}-\alpha_4\frac{s_{a_R}}{\mu_{a_R}}=0;$$

   with one real vanishing characteristic root, while other characteristic roots are negative;

3. *unstable (with one positive real root) if*

$$\alpha_{20}-\alpha_3\frac{s_{i_R}}{\mu_{i_R}}-\alpha_4\frac{s_{a_R}}{\mu_{a_R}}>0.$$

In order to study the local stability of E_P, we assume now $R_0 > 0$ in (5.4).
At E_P, b^* satisfies

$$\alpha_{20} - \alpha_3 i_R^* - \frac{\alpha_{20}}{\sigma} b^* - \alpha_4 a_R^* = 0$$

and (5.8) reduces to

$$\det \begin{pmatrix} \lambda + \frac{\alpha_{20}}{\sigma} b^* & \alpha_3 b^* & \alpha_4 b^* \\ -F_1(\lambda) & \lambda + \mu_{i_R} & 0 \\ -F_2(\lambda) & 0 & \lambda + \mu_{a_R} \end{pmatrix} = 0. \tag{5.9}$$

Therefore the study of local stability of E_P leads to the equation

$$\begin{aligned} &\lambda^3 + \lambda^2 \left(\mu_{a_R} + \mu_{i_R} + \frac{\alpha_{20}}{\sigma} b^* \right) \\ &+\lambda \left(\mu_{i_R}\mu_{a_R} + \alpha_3 b^* F_1(\lambda) + \alpha_4 b^* F_2(\lambda) + \frac{\alpha_{20}\mu_{a_R}}{\sigma} b^* + \frac{\alpha_{20}\mu_{i_R}}{\sigma} b^* \right) \\ &+b^* \left(\mu_{i_R}\mu_{a_R} \frac{\alpha_{20}}{\sigma} + \alpha_3 \mu_{a_R} F_1 + \alpha_4 \mu_{i_R} F_2(\lambda) \right) = 0. \end{aligned} \tag{5.10}$$

The information of the delays τ_1 and τ_2 is dependent on the choice of both delay kernels $\omega_1(\theta)$ and $\omega_2(\theta.)$ We assume the delay kernel w_1, referring to the delay in immune response, be uniform, and the delay kernel w_2, referring to the delay in adaptive response, be exponential.

$$w_1(\theta) = A, \quad F_1(\lambda) = \frac{A}{\lambda}\left(1 - e^{-\lambda\tau_1}\right), \qquad \theta \in [-\tau_1, 0], A \in \mathbb{R}^+, \tag{5.11}$$

$$w_2(\theta) = Ae^{k\theta}, \quad F_1(\lambda) = \frac{A}{\lambda + k}\left(1 - e^{(-\lambda+k)\tau_2}\right), \quad \theta \in [-\tau_2, 0], A, k \in \mathbb{R}^+. \tag{5.12}$$

Now note that if $\tau_1 = \tau_2 = 0$, then $F_1(\lambda) = F_2(\lambda) = 0$ and equation (5.10) becomes

$$\begin{aligned} &\lambda^3 + \lambda^2 \left(\mu_{a_R} + \mu_{i_R} + \frac{\alpha_{20}}{\sigma} b^* \right) \\ &+\lambda \left(\mu_{i_R}\mu_{a_R} + + \frac{\alpha_{20}\mu_{a_R}}{\sigma} b^* + \frac{\alpha_{20}\mu_{i_R}}{\sigma} b^* \right) \\ &+b^* \left(\mu_{i_R}\mu_{a_R} \frac{\alpha_{20}}{\sigma} \right) = 0, \end{aligned} \tag{5.13}$$

which has three negative roots.
Then it is possible to conclude that E_P is asymptotically stable at $\tau_1 = \tau_2 = 0$.
There exists the problem to find the delay values τ_1 and τ_2, if they exist, at which for increasing them E_P undergoes a stability switch. Substituting (5.11) in (5.13) the characteristic polynomial (5.13) is a fifth-order degree polynomial with delay-dependent coefficients [18]. In 2002 Beretta and Kuang have proposed in [3] a geometric stability switch criterion to study the occurrence of stability switches for characteristic equations

with one delay. In [29] and [60] Carletti applied this technique, providing examples of the numerical investigation of the stability and instability regions of the positive equilibrium for the immune system introduced by Beretta *et al.* in [58], *i.e.*, system (5.1) without the term $\alpha_4 b a_R$in the third equation . This system has a characteristic polynomial dependent only on one delay (τ_1). The extension of the geometric criterion to the case of two distinct delays is still an open problem. Then it is possible only to perform a qualitative study of the stability switches of E_P. To this end, in [18] and more recently in [61] the authors implement a heuristic argument applying a novel analysis known as uncertainty and sensitivity analysis to the deterministic system (5.1).
Our aim is to stochastically perturb the deterministic model (5.1) and then to investigate the stochastic stability of equilibria. On the hand in order to study the stochastic stability of the boundary equilibrium E_B we apply in the next Section of this thesis our theorems proved in the last Chapter and then compare the results with the stability conditions given by Theorem 5.2.1. On the other hand to study the presence of the stability switches of positive equilibrium point E_P, we implement in the last Chapter of this thesis a new algorithm to perform uncertainty and sensitivity analysis of the stochastic model and then compare the results obtained with the deterministic informations given by [18] and [61].

5.3 Stochastic version of the model and motivation

We now want to study the robustness of the equilibrium point E_B of the deterministic model (5.1) for the Human Immune response with respect to fluctuations due to considering the human body as a noisy environment. Then our aim is the investigation of the asymptotic stability properties of the equilibrium point of the stochastic version and then compare them with the properties of the same equilibrium in the deterministic case. This is a method used to validate the goodness of the original deterministic model and also to give a more realistic model describing the immune response model.

5.3.1 Stochastic immune response model

We perturb the system (5.1) by multiplicative noise, considering stochastic perturbations of white noise type, directly proportional to distances of variables from values of the equilibrium point $E_B = (x_U{}^*, x_I{}^*, b^*, i_R{}^*, a_R{}^*)$. This kind of noise formulation

was first introduced by Beretta *et al.* in [5]. The first use of this method to investigate the robustness of stability of an equilibrium point in the stochastic version, with the relative biological discussion, appeared in [6] and then was applied by other authors for different models in biology, ecology and medicine (*e.g.*, [7, 8]).
The system (5.1) is extended to the following form

$$\begin{aligned}
\mathrm{d}X_U(t) &= (s_U - \alpha_1 X_U(t)B(t) - \mu_{X_U}X_U(t))\,\mathrm{d}t + q_1(X_U(t) - {x_U}^*)\mathrm{d}W_1(t)\\
\mathrm{d}X_I(t) &= (\alpha_1 X_U(t)B(t) - \alpha_2 X_I(t)A_R(t) - \mu_{X_I}X_I(t))\,\mathrm{d}t + q_2(X_I(t) - {x_I}^*)\mathrm{d}W_2(t)\\
\mathrm{d}B(t) &= \left(\alpha_{20}B(t)\left(1 - \frac{B(t)}{\sigma}\right) - \alpha_3 B(t)I_R(t) - \alpha_4 B(t)A_R(t)\right)\mathrm{d}t\\
&\quad + q_3(B(t) - b^*)\mathrm{d}W_3(t) \qquad (5.14)\\
\mathrm{d}I_R(t) &= \left(s_{I_R} + \int_{-\tau_1}^{0} w_1(\theta)B(t+\theta)\mathrm{d}\theta - \mu_{I_R}I_R(t)\right)\mathrm{d}t + q_4(I_R(t) - {i_R}^*)\mathrm{d}W_4(t)\\
\mathrm{d}A_R(t) &= \left(s_{A_R} + \int_{-\tau_2}^{0} w_2(\theta)B(t+\theta)\mathrm{d}\theta - \mu_{A_R}A_R(t)\right)\mathrm{d}t + q_5(A_R(t) - {a_R}^*)\mathrm{d}W_5(t)
\end{aligned}$$

where q_i, $i = 1, \ldots, 5$, are positive constants, W_i, $i = 1, \ldots, 5$, are independent Wiener processes.
The perturbed system (5.14) belongs to the class of Stochastic Delay Differential Equations (SDDEs) with distributed memory. The point is to verify if E_B is robust with respect to environmental noise. In the next Section we study whether the boundary equilibrium is asymptotically mean square stable and we obtain conditions of stability in terms of tresholds on the parameter values and the amplitude of noise q_i, $i = 1, \ldots, 5$.

5.3.2 Stability of equilibria of stochastic model

We obtain stability conditions for the equilibrium point E_B of the mathematical model (5.14). Let us centre the system on the equilibrium point by the change of variable

$$\begin{aligned}
U_1 &= X_U - {X_U}^*,\\
U_2 &= X_I - {X_I}^*,\\
U_3 &= B - B^*,\\
U_4 &= I_R - {I_R}^*,\\
U_5 &= A_R - {A_R}^*;
\end{aligned}$$

then we have the following

$$
\begin{aligned}
dU_1(t) &= \left(-\alpha_1 U_3(t)U_1(t) - \mu_{X_U}U_1(t) - \alpha_1\frac{s_U}{\mu_{X_U}}U_3(t)\right)\mathrm{d}t + q_1U_1(t)\mathrm{d}W_1(t)\\
dU_2(t) &= \left(\alpha_1 U_1(t)U_3(t) + \alpha_1\frac{s_U}{\mu_{X_U}}U_3(t) - \alpha_2\frac{s_{A_R}}{\mu_{A_R}}U_2(t) - \mu_{X_I}U_2(t) - \alpha_2U_2(t)U_5(t)\right)\mathrm{d}t\\
&\quad +q_2U_2(t)\mathrm{d}W_2(t)\\
dU_3(t) &= \{\alpha_{20}U_3(t) - \alpha_{20}\frac{U_3(t)^2}{\sigma} - \alpha_3\frac{s_{I_R}}{\mu_{I_R}}U_3(t) - \alpha_4\frac{s_{A_R}}{\mu_{A_R}}U_3(t)\\
&\quad -\alpha_3U_3(t)U_4(t) - \alpha_4U_3(t)U_5(t)\}\mathrm{d}t + q_3U_3(t)\mathrm{d}W_3(t)\\
dU_4(t) &= \left(\int_{-\tau_1}^{0} w_1(\theta)U_3(t+\theta)\mathrm{d}\theta - \mu_{I_R}U_4(t)(t)\right)\mathrm{d}t + q_4U_4(t)\mathrm{d}W_4(t)\\
dU_5(t) &= \left(\int_{-\tau_2}^{0} w_2(\theta)U_3(t+\theta)\mathrm{d}\theta - \mu_{A_R}U_5(t)\right)\mathrm{d}t + q_5U_5(t)\mathrm{d}W_5(t)
\end{aligned}
$$

This is a stochastic system of 5 equations in 5 variables u_i, $i = 1, \ldots, 5$.

It is easy to see that the stability of the equilibrium point of (5.14) is equivalent to the stability of zero solution of the centred system.

After centring the system around the equilibrium, we linearise the centred system around $X^* \equiv 0$. We obtain the following system.

$$
\begin{aligned}
dU_1(t) &= \left(-\mu_{X_U}U_1(t) - \alpha_1\frac{s_U}{\mu_{X_U}}U_3(t)\right)\mathrm{d}t + q_1U_1(t)\mathrm{d}W_1(t)\\
dU_2(t) &= \left((-\alpha_2\frac{s_{A_R}}{\mu_{A_R}} - \mu_{X_I})U_2(t) + \alpha_1\frac{s_U}{\mu_{X_U}}U_3(t)\right)\mathrm{d}t\\
&\quad +q_2U_2(t)\mathrm{d}W_2(t)\\
dU_3(t) &= \left(\alpha_{20} - \alpha_3\frac{s_{I_R}}{\mu_{I_R}} - \alpha_4\frac{s_{A_R}}{\mu_{A_R}}\right)U_3(t)\mathrm{d}t + q_3U_3(t)\mathrm{d}W_3(t)\\
dU_4(t) &= \left(\int_{-\tau_1}^{0} w_1(\theta)U_3(t+\theta)\mathrm{d}\theta - \mu_{I_R}U_4(t)\right)\mathrm{d}t + q_4U_4(t)\mathrm{d}W_4(t)\\
dU_5(t) &= \left(\int_{-\tau_2}^{0} w_2(\theta)U_3(t+\theta)\mathrm{d}\theta - \mu_{A_R}U_5(t)\right)\mathrm{d}t + q_5U_5(t)\mathrm{d}W_5(t)
\end{aligned}
$$

If we define $F(t, U(t), Y(t))$ by

$$F(t,U(t),Y(t)) = \begin{pmatrix} -\mu_{X_U} U_1 - \alpha_1 \frac{s_U}{\mu_{X_U}} U_3(t) \\ \left(-\alpha_2 \frac{s_{A_R}}{\mu_{A_R}} - \mu_{X_I}\right) U_2(t) + \alpha_1 \frac{s_U}{\mu_{X_U}} U_3(t) \\ \left(\alpha_{20} - \alpha_3 \frac{s_{I_R}}{\mu_{I_R}} - \alpha_4 \frac{s_{A_R}}{\mu_{A_R}}\right) U_3(t) \\ Y_4(t) - \mu_{I_R} U_4(t) \\ Y_5(t) - \mu_{A_R} U_5(t) \end{pmatrix},$$

and $G(t, U(t), Y(t))$ by

$$G(t,U(t),Y(t)) = (q_1 U_1(t), q_2 U_2(t), q_3 U_3(t), q_4 U_4(t), q_5 U_5(t)),$$

where

$$U(t) = (U_1(t), U_2(t), U_3(t), U_4(t), U_5(t))$$

and

$$\begin{aligned} Y &= (Y_1, Y_2, Y_3, Y_4, Y_5) \\ &= \left(0, 0, 0, \textstyle\int_{-\tau_1}^{0} w_1(\theta) U_3(t+\theta) \mathrm{d}\theta, \int_{-\tau_2}^{0} w_2(\theta) U_3(t+\theta) \mathrm{d}\theta\right) \end{aligned}$$

then the system can be written in the following vectorial form

$$dU(t) = F(t, U(t), Y(t))\mathrm{d}t + G(t, U(t), Y(t))\mathrm{d}W(t).$$

Thus our system now has the form of equation (4.3) we studied in Chapter 4.

Theorem 5.3.1. *Let*

$$\begin{aligned} &\delta = \alpha_{20} - \alpha_3 \frac{s_{I_R}}{\mu_{I_R}} - \alpha_4 \frac{s_{A_R}}{\mu_{A_R}} \\ &k = \min\left\{ \frac{\mu_{X_U}}{2}, \mu_{X_I}, -\delta - \frac{\mu_{X_U}}{2} - \frac{1}{4} \frac{\mu_{A_R}}{\alpha_2 s_{A_R}} \left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2, \mu_{I_R}, \mu_{A_R} \right\} \\ &b_1 = \max\left\{q_1^2, q_2^2, q_3^2, q_4^2, q_5^2\right\} \\ &a_1 > 0, \quad a_1 \textit{very small positive number.} \end{aligned}$$

If the following condition

$$k > a_1 + \frac{b_1}{2} \tag{5.15}$$

is satisfied, then the trivial solution of the centred system is asymptotically mean-square stable.

Proof. We prove that the conditions of Theorem (4.2.6) are satisfied. In order to do this, we need to find $k > 0$ and three nonnegative numbers a_1, b_0, b_1 such that

$$U^T F(t, x, 0) \leq -k|U|^2 \tag{5.16}$$

$$|F(t, U, 0) - F(t, U, Y)| \leq a_1|Y| \tag{5.17}$$

and

$$|G(t, U, Y)|^2 \leq b_0|U|^2 + b_1|Y|^2 \tag{5.18}$$

for all $t \geq 0$ and $U, Y \in \mathbb{R}^d$, with the following condition satisfied

$$k > a_1 + \frac{1}{2}(b_0 + b_1) \tag{5.19}$$

After substitution of the functions terms, we obtain the following inequalities.

$$\begin{aligned}
&U^T F(t, U, Y) = f_1U_1 + f_2U_2 + f_3U_3 + (-\mu_{I_R}U_4)U_4 + (-\mu_{A_R}U_5)U_5 \\
&= \left(-\mu_{X_U}U_1 - \alpha_1\frac{s_U}{\mu_{X_U}}U_3\right)U_1 + \left((-\alpha_2\frac{s_{A_R}}{\mu_{A_R}} - \mu_{X_I})U_2 + \alpha_1\frac{s_U}{\mu_{X_U}}U_3\right)U_2 \\
&\quad + \left((\alpha_{20} - \alpha_3\frac{s_{I_R}}{\mu_{I_R}} - \alpha_4\frac{s_{A_R}}{\mu_{A_R}})U_3\right)U_3 - \mu_{I_R})U_4^2 - \mu_{A_R}U_5^2 \\
&= -\mu_{X_U}U_1^2 + \left(-\alpha_2\frac{s_{A_R}}{\mu_{A_R}} - \mu_{X_I}\right)U_2^2 + \delta U_3^2 - \mu_{I_R}U_4^2 - \mu_{A_R}U_5^2 - \alpha_1\frac{s_U}{\mu_{X_U}}U_3U_1 \\
&\quad + \alpha_1\frac{s_U}{\mu_{X_U}}U_3U_2 \\
&\leq -\mu_{X_U}U_1^2 + \left(-\alpha_2\frac{s_{A_R}}{\mu_{A_R}} - \mu_{X_I}\right)U_2^2 + \delta U_3^2 - \mu_{I_R}U_4^2 - \mu_{A_R}U_5^2 \\
&\quad + \mu_{X_U}\left(\frac{1}{2}U_3^2 + \frac{1}{2}U_1^2\right) + \alpha_1\frac{s_U}{\mu_{X_U}}\left(\frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\alpha_1\frac{s_U}{\mu_{X_U}}U_3^2 + \alpha_2\frac{s_{A_R}}{\mu_{A_R}}\frac{\mu_{X_U}}{\alpha_1 s_U}U_2^2\right) \\
&= -\left(\frac{\mu_{X_U}}{2}\right)U_1^2 - (\mu_{X_I})\,U_2^2 - \left(-\delta - \frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2\right)U_3^2 - (\mu_{I_R})\,U_4^2 \\
&\quad - (\mu_{A_R})\,U_5^2 \\
&\leq -k|U|^2
\end{aligned}$$

where

$$k = \min\left\{\frac{\mu_{X_U}}{2}, \mu_{X_I}, -\delta - \frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2, \mu_{I_R}, \mu_{A_R}\right\}.$$

We applied the elementary inequality

$$a^{p-1}b \leq \frac{\epsilon_1(p-1)}{p}a^p + \frac{1}{p\epsilon_1^{p-1}}b^p),$$

for $a, b \geq 0, \epsilon_1 > 0, p \geq 2$, obtaining the following inequalities

$$U_3U_1 \leq \frac{1}{2}U_3^2 + \frac{1}{2}U_1^2 \qquad \epsilon_1 = 1,\ p = 2,$$
$$U_3U_2 \leq \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\alpha_1\frac{s_U}{\mu_{X_U}}U_3^2 + \alpha_2\frac{s_{A_R}}{\mu_{A_R}}\frac{\mu_{X_U}}{\alpha_1 s_U}U_2^2 \qquad \epsilon_1 = 2\alpha_2\frac{s_{A_R}}{\mu_{A_R}}\frac{\mu_{X_U}}{\alpha_1 s_U},\ p = 2$$

which we used above. In the last inequality we used the hypothesis of the theorem, obtaining that

$$-\delta - \frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2 > 0 \tag{5.20}$$

and, consequently,

$$k > 0.$$

Also we have, for $a_1 > 0$ (very small), that

$$|F(t, U, 0) - F(t, U, Y)| = y_4 + y_5 \leq a_1|Y|$$

and

$$|G(t, U, Y)|^2 = q_1^2U_1^2 + q_2^2U_2^2 + q_3^2U_3^2 + q_4^2U_4^2 + q_5^2U_5^2 \leq b_1|U|^2$$

where

$$b_1 = \max\{q_1^2,\ q_2^2,\ q_3^2,\ q_4^2,\ q_5^2\}.$$

In this way conditions (5.16), (5.17), (5.18) and (5.19), with $b_0 = 0$, are satisfied and it is possible to apply Theorem 4.2.6. Then we have that the trivial solution of the linearised system is exponentially mean-square stable. In virtue of Theorem 4.3.8, the proof is complete. □

Note that the conditions that we required for the parameters during the proof of Theorem 5.3.1 are consistent with the range defined in the Table 5.1.
We then verified that the asymptotically stability of the boundary equilibrium E_B is preserved, under conditions of Theorem 5.3.1, in the stochastic setting. The theoretical results obtained by Theorem 5.3.1 confirm the robustness of the boundary equilibrium point (considering very small noise) and give us sufficient conditions for the asymptotic mean-square stability quite similar to that one showed by Beretta *et al.* for the deterministic case. We relegate a detailed biological discussion of this results to the last chapter of this Thesis.

6

Numerical methods and simulations

Our aim in this chapter is to perform simulations of the stochastic model of human immune response in order to illustrate the stability results obtained in the last chapter We perform original simulation studies of the solution of equation (5.14). A biological discussion of information obtained is also provided.

Before we discuss the simulations performed, we give a brief overview of numerical methods for stochastic differential equations (with and without delay). As introductory textbooks on numerical theory for SODEs, one can refer to Kloden and Platen [62] and Artemiev [63]. More advanced material on SODEs is presented, for instance, in Milstein [64, 65] and Buckwar [66]. On numerical analysis for SDDEs we refer to material presented in Mao [67, 68], in Buckwar [66], and Baker and Buckwar [69].

6.1 Numerical methods for SODEs

Consider the d-dimensional stochastic differential equation of Itô type

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW(t), \quad t \in [0, T], \tag{6.1}$$

with initial condition

$$X(0) = X_0,$$

where W is an m-dimensional Wiener process and $f : [0, T] \times \mathbb{R}^d \to \mathbb{R}^d$ and $g : [0, T] \times \mathbb{R}^d \to \mathbb{R}^{d\times m}$. It is known that explicit solutions of SODEs are rare, thus it

is necessary to develop numerical approximation methods. We consider discrete time approximation methods for SODEs, based on the discretisation of the time interval $[0, T]$ as

$$t_0 = 0 < t_1 < t_2 < \cdots < t_n < \cdots < t_N = T, \tag{6.2}$$

using an equidistant step-size $h = T/N$, such that $t_n = n \cdot h$.

6.1.1 Euler-Maruyama method

The simplest stochastic numerical scheme for Itô SODE (6.1) is the Euler-Maruyama (EM) method, which was first studied by Maruyama in 1955 [70] and it results to be really suited for implementation on computers. The EM method is given by the recursive equation

$$Y_{n+1} = Y_n + f(Y_n)h + g(Y_n)\Delta W_n \tag{6.3}$$

where Y_n is the numerical approximation of the solution of (6.1) at time t_n, $X(t_n)$, on the grid (6.2) with step-size h, and $Y_0 = X_0$. Here $\Delta W_n = W(t_{n+1}) - W(t_n)$, $n = 0, 1, 2, \ldots, N$ denote the increments of the Wiener process in the time interval $[t_n, t_{n+1}]$ and are represented by independent $N(0, h)$ Gaussian random variables with mean zero and variance h. To simulate a realisation of the Euler approximation it is necessary to generate the independent random variables involved. They can be generated by pseudo-random number generators and the two most popular methods are the are Box-Muller method or Polar-Marsaglia method [71, 72].

6.1.2 Strong and weak convergence

In (stochastic) numerical analysis, the order of convergence plays a crucial role in the design of numerical algorithms and the choice of the convergence criterion depends on the type of the problem. These can be identified by whether one requires approximations to the sample paths, or approximations to the corresponding distributions. When the task is to simulate trajectories of the solution process accurately, we measure the approximation error in the mean-square norm and thus consider mean-square as strong convergence of a numerical method. For approximating statistical information of the solution process, weak convergence is an appropriate type of convergence to address.

The following criteria allow to classify numerical methods according to their strong order γ of convergence. For a random variable Z with bounded second moment, we

define the norm $\|Z\|_{L_2}$ to be $\|Z\|_{L_2} := (\mathbb{E}|Z|^2)^{\frac{1}{2}}$, where $|\cdot|$ is the Euclidean norm on $\mathbb{R}^d$. A discrete time approximation Y of the exact solution X of an SODE of the form (6.1), after N steps with constant step-size $h = \frac{T}{N}$, *converges in the strong sense* with order $\gamma \in (0, \infty)$ if there exists a constant $C < \infty$ independent of h and such that

$$\max_{0 \leq n \leq N} \|X(t_n) - Y_n\|_{L_2} \leq Ch^\gamma$$

for all $h \to 0$.

On the other hand, Y is said to converge in the weak sense with order $\gamma \in [0, \infty)$ if, for any function test $g : \mathbb{R}^d \to \mathbb{R}$, there exists a constant $C < \infty$ such that

$$\|\mathbb{E}(g(X(T)) - \mathbb{E}(g(Y_N))\| \leq Ch^\gamma$$

for all step-sizes $h \in (0, 1)$, provided that these functionals exist. Since is much easier to implement numerical methods constructed with respect to the weak convergence criterion than those required by the strong convergence criterion, it is convenient in any practical simulation to try, if possible, to identify directly the task at hand as being one that requires a weak approximation method. The EM method has strong order of convergence $\gamma = 0.5$ and weak order of convergence $\gamma = 1$. Note that the order of accuracy of a method may be increased for SODEs of a particular type. However, in the case of systems with additive noise, the EM method has strong order 1 .

6.1.3 Numerical stability and stiffness

While the concepts of strong and weak convergence concern the accuracy of a numerical method over a finite interval $[0, T]$ for the limit of $h \to 0$, the concept of *numerical stability* of a one-step method concerns the property of errors to remain bounded with respect to an initial error for any SODE of the form (6.1) with drift coefficients f satisfying global Lipschitz conditions.

There are two well-known stability definitions of a numerical method: *mean-square* (MS) and *almost sure* stability. Almost sure and mean-square stability of the EM method were studied by Higham in [73]. It turns out, as in deterministic case, that the Euler-Maruyama method is simple but often inefficient and with poor stability properties. Better stochastic numerical methods are Runge-Kutta methods or multi-step methods [74].

6.2 Numerical methods for SDDEs

In the numerical analysis of differential equations with delay (deterministic and stochastic), the central problem is the representation of the memory term. In the deterministic case all standard ODE methods have been extended to DDEs, with for example Hermite interpolation or continuous extension of Runge-Kutta methods or quadrature approach with memory functionals. A complete introduction to the argument of numerical methods and computer packages designed for DDEs is given by [75]. Only recently has been conceived the numerical analysis for the stochastic case. In 2000 Baker and Buckwar in [69] provided a theorem on mean-square convergence for explicit one-step schemes applied to SDDEs with discrete delays and global Lipschitz coefficient functions. However the main method used is the Euler-Maruyama (EM) method, i.e the stochastic version of The Euler approach.

In 2003 Maoand Sabanis in [68] applied the EM method to SDDEs with variable delays and local Lipschitz conditions on the coefficient functions. Later Mao applied the EM method to SFDEs with the general memory term X_t, where this was linearly interpolated, under local and global Lipschitz conditions on the coefficient functions [67]. In 2004 Hu, Mohammed and Yan developed and analysed a Milstein scheme for SFDEs with discrete delays [76].

A systematic approach to the analysis of mean-square convergence of drift-implicit numerical schemes under global Lipschitz conditions on the coefficient functions was given in 2006 by Buckwar in [77, 78]. Such numerical methods can be successfully applied to stochastic equations with discrete, multiple, variable or distributed delays, in the scalar or multidimensional case driven by single or d-dimensional Wiener processes. Since we are interested on the application to the stochastic immune model 5.14, we recall the main results by Buckwar appearing in [77] for stochastic delay differential equations (SDDEs) with distributed delays.

6.2.1 SDDEs with distributed delays

We consider the SDDE with a distributed memory term of the form

$$\begin{aligned} dX(t) = & F\left(t, X(t), Y(s)\right)) \, dt \\ & + G\left(t, X(t), Y(s)\right)) \, dW(t) \end{aligned} \tag{6.4}$$

with initial data

$$X(s) = \psi(s) \qquad s \in J := [-\tau, 0], \quad \tau > 0.$$

In (6.4) $Y(t)$ represents the memory term of this form

$$Y(t) = \int_{-\tau}^{0} K(t, s, X(t+s))dt \tag{6.5}$$

with initial data

$$X(s) = \psi(s) \qquad s \in J := [-\tau, 0], \quad \tau > 0.$$

After defining a family of meshes on the interval $[0, T]$ as $\mathfrak{T}_h^N := \{0 = t_0 < t_1 < t_2, \cdots < t_N\} \subseteq [0, T]$, with $t_n = nh,\ n = 0, \ldots, N,\ hN \leq T,\ N \in \mathbb{N}$, we require, given the time lag τ, that

$$h = \tau/N_\tau, \qquad N_\tau \in \mathbb{N}. \tag{6.6}$$

On $\mathfrak{T}_h^N$ we consider strong approximations $\widetilde{X}_n$ of the solution to SDDE (4.3) using the Θ-*Maruyama-method* given by

$$\begin{aligned} \widetilde{X}_n =& \widetilde{X}_{n-1} \ + \ h\left[\Theta\ F(t_n, \widetilde{X}_n, \widetilde{Y}_n) + (1-\Theta)F(t_{n-1}, \widetilde{X}_{n-1}, \widetilde{Y}_{n-1})\right] \\ &+ \sum_{j=1}^{d} G(t_{n-1}, \widetilde{X}_{n-1}, \widetilde{Y}_{n-1}) I_j^{t_{n-1}, t_n} \end{aligned} \tag{6.7}$$

where $\Theta \in [0, 1]$ and $I_{(j_1, j_2, \ldots, j_l)}^{t, t+h} = \int_t^{t+h} \int_t^{s_l} \ldots \int_t^{s_2} \ dW_{j_1}(s_1) \ldots dW_{j_l}(s_l)$, $j_i \in \{0, 1, \ldots, d\}$, $i = 1, \ldots, l$, are multiple Wiener integrals. The initial values are given by $\widetilde{X}_i := \Psi(t_i)$ for $i \leq 0$ and the term $\widetilde{Y}_m$ provides an approximation to the integral $Y(t_m)$. Methods of the class (6.7)) are implicit in the drift term for $\Theta \in (0, 1]$. In a stochastic setting we can choose different quadrature rules for the drift and diffusion coefficients. In this thesis we will use for the drift coefficient an explicit scheme, the *composite Euler* rule

$$\widetilde{Y}_m^E = h \sum_{\ell=m-N_\tau}^{m-1} K(t_m, t_\ell - t_m, \widetilde{X}_\ell), \ m \geq 0 \tag{6.8}$$

and for the diffusion coefficient an implicit scheme, the *composite trapezium* rule

$$\widetilde{Y}_m^T = h \sum_{\ell=m-N_\tau}^{m}{}'' K(t_m, t_\ell - t_m, \widetilde{X}_\ell), \ m \geq 0. \tag{6.9}$$

where the notation $\sum''$ means that the first and the last term in the sum are to be halved.

This choice of quadrature is quite useful in the case of a small noise coefficient [77].

Definition 6.2.1. *The approximations* $\{\widetilde{X}_n\}$ *to the solution* X *of* (6.4) *are said to be* mean-square consistent *with order* p $(p > 0)$ *if the following estimates hold:*

$$\begin{aligned} \max_{t_n \in \mathcal{T}_h^N} \|\mathbb{E}(\,\delta_n | \mathcal{A}_{t_n})\|_{L_2} &\leq C\ h^{p+1} \quad as\ h \to 0 \\ \max_{t_n \in \mathcal{T}_h^N} \|\delta_n\|_{L_2} &\leq C\ h^{p+1/2} \quad as\ h \to 0, \end{aligned}$$

where δ_n *is the local error, and the generic constant* C *does not depend on* h*, but may depend on* T *and the initial data.*

With *local error* we refer at the defect that is obtained when the exact solution values are inserted into the numerical scheme [78].

Definition 6.2.2. *The approximations* $\{\widetilde{X}_n\}$ *to the solution* X *of equation* (6.1)*, defined on* $\mathcal{T}_h^N$ *with the delay* τ *multiple of the step-size* h*, are said to be* mean-square convergent with order p*, on the mesh-points, when*

$$\max_{t_n \in \mathcal{T}_h^N} \|X(t_n) - \widetilde{X}_n\|_{L_2} \leq C\ h^p \quad as\ h \to 0.$$

Under suitable conditions on the drift and diffusion coefficients the Θ-Maruyama method (6.7) is mean-square consistent with order $p = 1/2$ [77]. Thus, if the Θ-Maruyama method is mean-square consistent and the increment functions on the right-hand side of (6.7) satisfy uniform Lipschitz conditions, then it is mean-square convergent. The order of consistency implies the order of convergence [77].

6.3 Numerical simulations of stochastic immune response model

In this section we carry out some simulations of the stochastic model (5.14) in order to illustrate the stability results obtained in Chapter 5. We simulate the solutions in the case of multiplicative noise according to (5.14). Following the numerical methods developed by Buckwar in [77], we performed the simulations in the Matlab environment using the θ-Maruyama-method and the trapezoidal method for the integrals. We used the value of the parameters and the initial conditions shown in Table 6.2 and Table 6.1. We simulate the dynamics of the stochastic non-linear system (5.14), choosing for both integrals uniform delay kernels. First of all, by Theorem 5.3.1 we expect that asymptotic mean-square stability for the stochastic non-linear model is reached only

for quite small noise coefficients. We simulated (fig. 6.1) the solution of the stochastic system, choosing the values of parameters in Table 6.2 (according with the conditions of the Theorem 5.3.1) and different coefficients of noise (for convenience we used the same value for all five equations). We observed that the noise must be quite small, otherwise the solution explodes (fig. 6.1(c)). The numerical simulations illustrate that the asymptotic mean-square stability of E_B depends on the amplitudes of the noise terms q_i, which must be quite small, according to the conditions of the Theorem 5.3.1.

Name	**Value**
$X_U(0)$	10^3
$X_I(0)$	0
$B(0)$	20
$I_R(0)$	$4e^3$
$A_R(0)$	10^3

Table 6.1: Initial conditions used for the simulations.

Name	**Value**	**Name**	**Value**
α_1	10^{-3}	σ	10^5
α_2	10^{-3}	μ_{X_U}	0.011
α_3	10^{-4}	μ_{X_I}	0.011
α_4	10^{-5}	μ_{I_R}	0.11
α_{20}	.7	μ_{A_R}	0.33

Table 6.2: Parameters values used for the simulations.

In the deterministic case, by Theorem 5.2.1, we have that the boundary equilibrium E_B is asymptotically stable if $\delta < 0$. From the Theorem 5.3.1 we obtained a similar condition about δ, in fact from (5.20), a sufficient condition for the stability is $\delta < -\frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2 < 0$. The analysis of the simulations of the solution of the stochastic model, using the values of the parameters defined in Table 6.2 and the noise terms very small, confirms what Beretta *et al.* found for the deterministic case (see the final biological discussion in [58]), *i.e.*, there exists a relation between $I_R(0)$ and the parameter α_{20}, which determines the final infection outcome. In fact we simulated

several paths of the solution, choosing for the first one $I_R(0)$ dependent from a constant C ($I_R(0) = Ce^3$). By condition (5.20), we expect that this constant C could not be less than $C_1 = \left(\alpha_{20} + \frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2 - \alpha_4\frac{s_{A_R}}{\mu_{A_R}}\right)\frac{1}{\alpha_3 10^3}$. We observed that this result remains true during the simulations. In Fig. 6.2 it is possible to see how the oscillatory behaviour changes if we have the constant C less than C_1 defined above. With a more accurate analysis is possible to notice that, since we worked with the model including a term representing direct bacterial killing by adaptive immunity, there exists also a relation between $A_R(0)$ and the parameter α_{20}, describing the bacterial load. This last information is consistent with the most recent theory on the deterministic case [18]. To numerically verify the mean-square stability of the boundary equilibrium E_B under the conditions of Theorem 5.3.1, we implemented an algorithm where we simulate M paths of every populations $X(t)$. Then we approximate as an average the expectation

$$\mathbb{E}|X(t) - E_B|^2,\ t \geq 0.$$

By defining

$$\delta = \alpha_2 0 - \alpha_3(s_{I_R}/\mu_{I_R}) - \alpha_4(s_{A_R}/\mu_{A_R})$$

and

$$L = -\delta - \mu_{X_U}/2 - (1/4)(\mu_{A_R}/(\alpha_2 s_{A_R}))((\alpha_1 s_U)/\mu_{X_U})^2$$

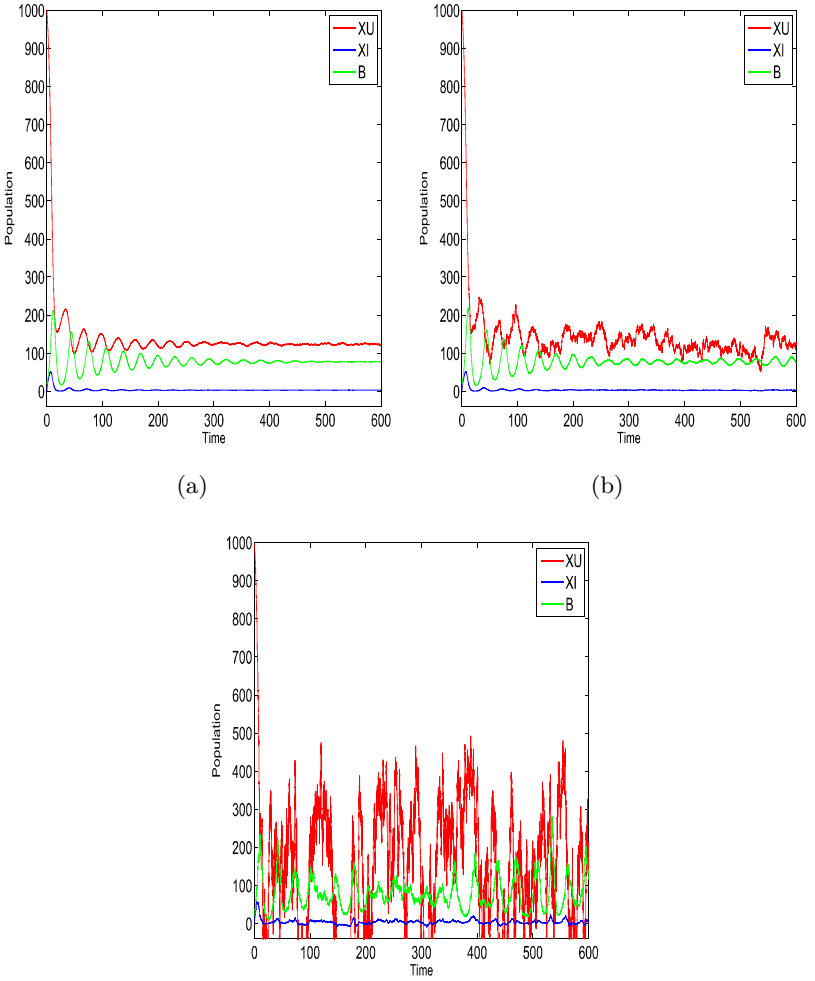
and considering small noise, we are going to consider two cases

1. for $\delta < 0$, $L > 0$ E_B is asymptotically mean-square stable,
2. for $\delta < 0$, $L < 0$ E_B is not asymptotically mean-square stable.

The first case is consistent with the stability conditions of Theorem 5.3.1, instead the second case does not satisfy the conditions of Theorem 5.3.1. The results of our simulations indicate that for the first case we have asymptotic mean-square stability of E_B for every component, see Figure 6.4(a). In the second case the first component is not asymptotically mean-square stable any more, see Figure 6.4(b). In Figure 6.3 we show the case when conditions are satisfied. The solution $X(t)$ of system (5.14) is simulated under the parameter values satisfying the conditions of Theorem 5.3.1. The dotted straight lines represent the constant solution at E_B. We can conclude that from the numerical simulations we obtained a verification of the sufficient stability conditions established in Theorem 5.3.1.

6.4 Biological discussion

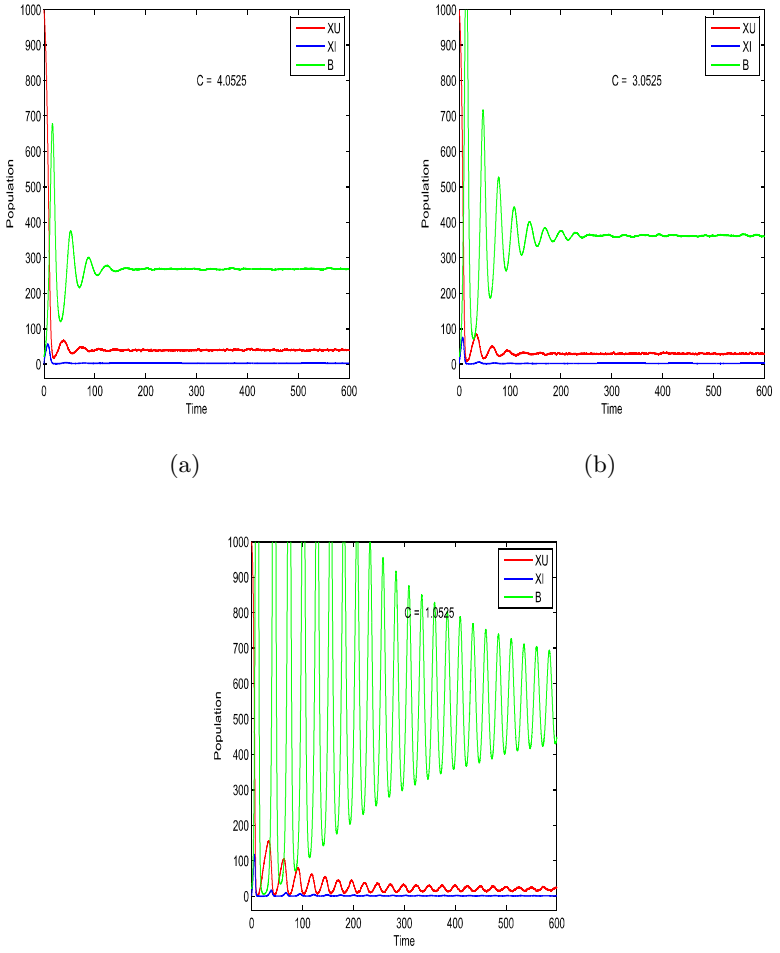
We analysed the robustness of the boundary equilibrium point of the deterministic model (5.1) from Beretta, Kirshner and Marino [18] with respect the fluctuations, considering the human body as a noisy environment. We introduced a stochastic perturbations of white noise type, directly proportional to distances of variables from values of equilibrium point. Then we linearised the stochastic system and centred the system around the null solution. Applying Theorem 4.3.8 of first approximation, it was possible to establish a sufficient condition for the asymptotic mean-square stability of the equilibrium of the non-linear stochastic model. The theoretical results obtained (illustrated by numerical simulations) confirm the robustness of the boundary equilibrium point (considering very small noise) and give us a sufficient condition for the asymptotic mean-square stability quite similar to that one shown by Beretta *et al.* for the deterministic case. From the biological point of view, the condition for the asymptotic stability of equilibrium E_B in Theorem 5.3.1 showed us a relation between the concentration of the initial immune cells at the uninfected equilibrium point $I_R(0)$ and the threshold of the population of Bacteria $\alpha_2 0$. The product of $I_R(0)$ and α_3, *i.e.*, the rate of killing of Bacteria due to the immune response, determines the strength of the innate immune system defence against the presence of bacteria; the parameter α_{20} measures the strength of the bacteria's offensive. From condition (5.20) we can examine the strength of the immune system against the bacterial hostile action. In fact the bacteria will be cleared if the strength of the immune response is not weaker than the bacteria's offensive strength (see the inequality between $I_R(0)$ and α_{20} in Section 6.3). This biological result fits with biological discussion about the deterministic model described by Beretta *et al.* in [58]. We can think it is possible to have a similar biological result about the strength of the adaptive response, as it is easy to see a possible relation between $A_R(0)$ and α_{20}, always from condition (5.20). We conclude that studying stability properties of equilibrium E_B, which represents the uninfected state obtained by a successful immune response of the host, the clearance of bacteria is a structural property of the host as the initial number cells $I_R(0)$ and $A_R(0)$ and the virulence factor of the bacteria expressed by the parameter $\alpha_2 0$.



(a) (b)

(c)

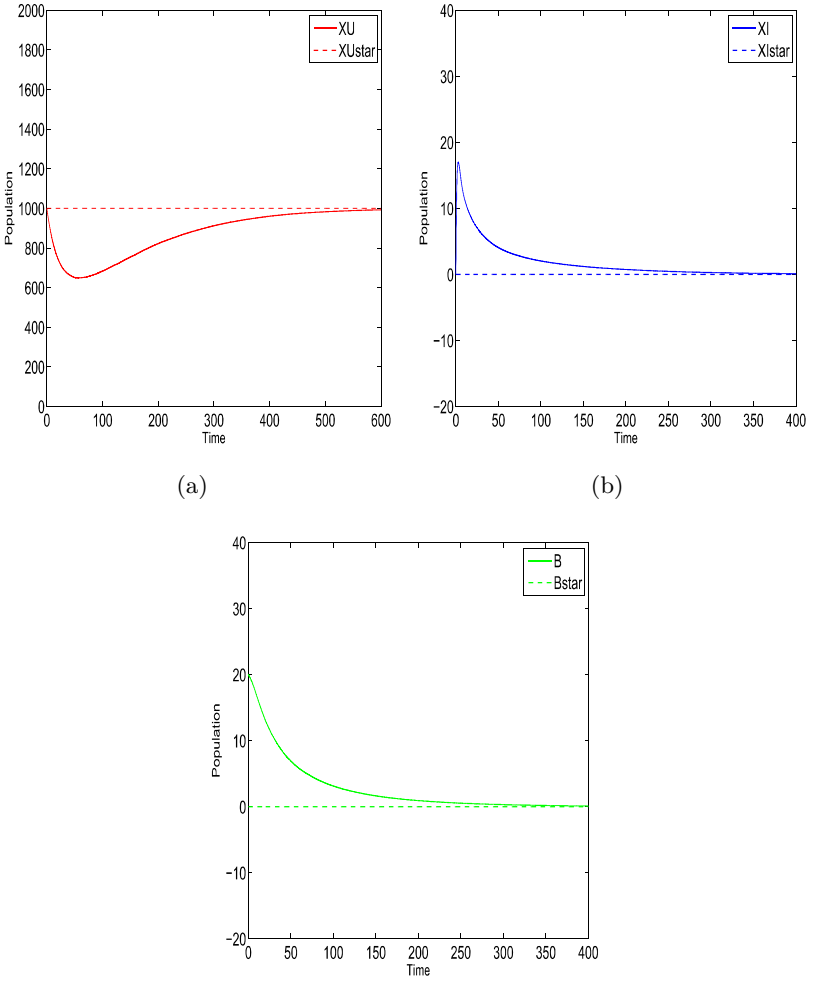
Figure 6.1: Numerical simulation of one path of the solution (X_U, X_I, B, I_R, A_R) (vs t) of model (5.14) for the human immune response model with multiplicative noise with $\tau_1 = 1$, $\tau_2 = 10$. The initial condition is $(X_U(0), X_I(0), B(0), I_R(0), A_R(0)) = (10^3, 0, 20, 10^3, 10^3)$ and $q_i = q$,for $i = 1, \ldots, 5$.
(a) $q = 0.001$; (b) $q = 0.01$; (c) $q = 0.11$.



(a) (b)

(c)

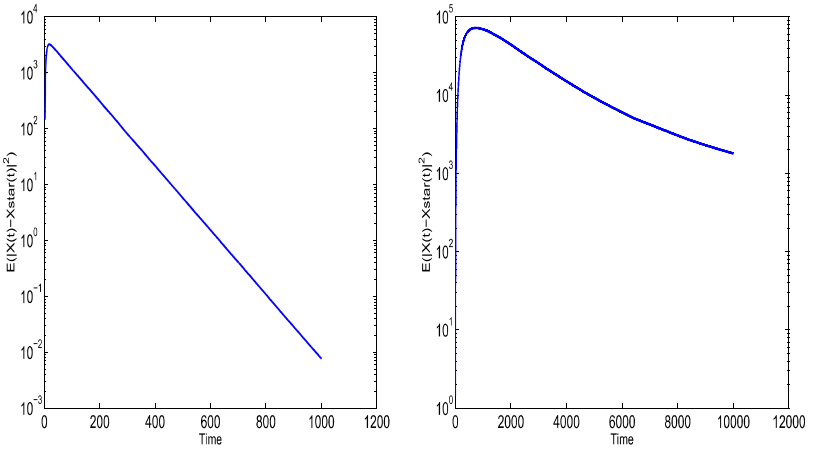
Figure 6.2: Numerical simulation of one path of solution (X_U, X_I, B, I_R, A_R) (vs t) of model (5.14) for the human immune response model with multiplicative noise with $\tau_1 = 4$, $\tau_2 = 5$. The initial condition is $(X_U(0), X_I(0), B(0), I_R(0), A_R(0)) = (10^3, 0, 20, C \times 10^3, 10^3)$.
(a) $\alpha_{20} = 0.7, C = C_1$; (b) $\alpha_{20} = 0.7, C = C_1 - 1$; (c) $\alpha_{20} = 0.7, C = C_1 - 3$,
where $C_1 = \left(\alpha_{20} + \frac{\mu_{X_U}}{2} - \frac{1}{4}\frac{\mu_{A_R}}{\alpha_2 s_{A_R}}\left(\frac{\alpha_1 s_U}{\mu_{X_U}}\right)^2 - \alpha_4 \frac{s_{A_R}}{\mu_{A_R}}\right)\frac{1}{\alpha_3 10^3}$



(a) (b)

(c)

Figure 6.3: Numerical simulation of solutions of model (5.14) for the human immune response model with multiplicative noise with $\tau_1 = 1$, $\tau_2 = 10$. The initial condition is $(X_U(0), X_I(0), B(0), I_R(0), A_R(0)) = (10^3, 0, 20, 7 \times 10^3, 10^3)$ and $q_i = q = 0.001$,for $i = 1, \ldots, 5$. The dotted straight line represent the constant solution E_B.
(a) X_U versus time t; (b) X_I versus time t; (c) B versus time t.



(a) (b)

Figure 6.4: Numerical simulation of 10 paths of solution (X_U, X_I, B, I_R, A_R) (vs t) of model (5.14) for the human immune response model with multiplicative noise with $\tau_1 = 1$, $\tau_2 = 10$. The initial condition is $(X_U(0), X_I(0), B(0), I_R(0), A_R(0)) = (10^3, 0, 20, 7 \times 10^3, 10^3)$ and $q_i = q = 0.001$,for $i = 1, \ldots, 5$.
(a) $delta < 0$, $L > 0$; (b) $delta < 0$, $L < 0$,
where $\delta = \alpha_2 0 - \alpha_3(s_{I_R}/\mu_{I_R}) - \alpha_4(s_{A_R}/\mu_{A_R})$, $L = -\delta - \mu_{X_U}/2 - (1/4)(\mu_{A_R}/(\alpha_2 s_{A_R}))((\alpha_1 s_U)/\mu_{X_U})^2$

7

Uncertainty and sensitivity analysis of a stochastic immune model

In this last chapter we implement Matlab codes to perform the uncertainty and sensitivity analysis of our stochastic immune model. We investigate the uncertainty in the model output generated from uncertainty in parameter inputs. We also obtain a classification of suitable thresholds of the delays to predict the stability switch of the positive equilibrium point of our stochastic immune model. We conclude with a discussion of biological implications of these results to carrying out research on the human immune response.

7.1 Introduction

The knowledge of biological phenomena is often incomplete because experimental measures are lacking and variances in many of the parameters values occur due to extensive variability in the data. Uncertainty and Sensitivity Analysis helps to characterize and control these uncertainties associated with a model. Uncertainty analysis (UA) quantifies the uncertainty in the outcome of a model produced by the uncertainty in parameter inputs. Sensitivity Analysis (SA) has the complementary role of investigating what parameters contribute most to the outcome value [79, 80]. Several methods have been developed to deal with US analysis: differential analysis, response surface methodol-

ogy, Monte Carlo (MC) analysis, and variance decomposition methods [79, 81]. For the purpose of this thesis we are interested in the Latin hypercube sampling (LHS) method for what concerns the uncertainty analysis and in the Partial Rank Correlation Coefficient (PRCC) and Extended Fourier amplitude test (eFAST) for the sensitivity analysis. First of all we briefly describe these techniques, then we illustrate how they have been applied to the deterministic model (5.1). Our aim is to apply this kind of analysis to our stochastic model and then compare the results with the deterministic one.

7.2 Uncertainty and sensitivity analysis methods

7.2.1 Uncertainty analysis: the LHS technique

Uncertainty analysis is a method to quantify the degree of confidence in the existing experimental data and parameter estimates. Several sampling strategies can be implemented to perform UA, but the most popular sampling scheme for UA is the LHS algorithm. Latin hypercube sampling, introduced in 1979 by McKay *et al.* [82], is a stratified sampling without replacement. The random parameter distributions are divided into equal probability intervals and then are sampled. The integer N is called the *sample size*. The sampling is performed by choosing a probability density function for each parameter, depending on a priori information (*i.e.*, normal, uniform, lognormal). Then a matrix (called the LHS matrix) is generated, which consists of k columns corresponding to the number of varied parameters and N rows for the number of simulations: hence, N model solutions are simulated, where each the simulations use the combination of parameter values given by the ith row of the LHS matrix. The model output of interest is collected for each model simulation. The sample size should be at least $k+1$, but the sampling is more accurate for larger values of N. By this method it is possible to identify all relevant and distinct stable numerical solutions for the given range of parameters.

7.2.2 Sensitivity analysis: PRCC and eFAST methods

The objective of the sensitivity analysis is to identify critical inputs (parameters and initial conditions) of a model a quantify how input uncertainty affects the outcome and stability switches.. The local SA investigates the impact on model output when

input factors (parameters or initial conditions) change only very little with respect to the nominal values. But in biological models the input factors are often with a not so little uncertainty and then global SA techniques are necessary. These global procedures are usually called *sampling-based methods*. We will focus only on PRCC and eFAST methods.

Examine scatter plots is the natural starting point in the analysis with sampling-based methods. For linear relationship measures the most used methods are the Pearson correlation coefficient (CC), partial correlation coefficients (PCCs), and standardized regression coefficients (SRC). For nonlinear but monotonic relationships between outputs and inputs, the measures that give best results are based on rank transforms such as Spearman rank correlation coefficient (RCC), partial rank correlation coefficient (PRCC), and standardized rank regression coefficients (SRRC). For nonlinear non-monotonic trends the best choice is to apply methods based on decomposition of model output variance. Examples of these methods are the Sobol method, the Fourier amplitude sensitivity test (FAST) and its extended version (eFAST).

We now give a brief description only of PRCC and eFAST methods, for details of the other techniques we refer the reader to [79].

Correlation provides a measure of the strength of a linear association between an input and an output [61]. A Pearson correlation coefficient $r_{x_j y}$ between input x_j and output y is given by

$$r_{x_j y} = \frac{\mathrm{Cov}(x_j, y)}{\sqrt{\mathrm{Var}(x_j)\mathrm{Var}(y)}} = \frac{\sum_{i=1}^{N}(x_y - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{N}(x_y - \bar{x})^2 \sum_{i=1}^{N}(y_i - \bar{y})^2}} \tag{7.1}$$

where $j = 1, ..., k$, $\mathrm{Cov}(x_j, y)$ represents the covariance between x_j and y, $\mathrm{Var}(x_j)$ and $\mathrm{Var}(y)$ are the variance of x_j and y, respectively, and $\bar{x}$ and $\bar{y}$ are the respective sample means.

Correlation coefficients vary between -1 and 1. Partial correlation characterizes the linear relationship between input and output when the linear effects on the output of the remaining inputs are not considered. Then the Partial correlation coefficient (PCC) is the CC between the two residual $(x_j - \hat{x}_j)$ and $(y - \hat{y})$, where $\hat{x_j}$ and $\hat{y}$ are the following linear regression models:

$$\hat{x}_j = c_0 + \sum_{p=1, p=j}^{k} c_p x_p \qquad \text{and} \qquad \hat{y} = b_0 + \sum_{p=1, p=j}^{k} b_p x_p \tag{7.2}$$

The partial rank correlation coefficient ($PRCC$) performs a partial rank correlation on rank-transformed data: x_j and y are first rank transformed and then the linear regression models are built by (7.2). PRCC is a robust sensitivity measure for nonlinear but monotonic relationship between input and output. By combining LHS with PRCC, we can assess the sensitivity of our outcome variable to parameter variation.
It is possible to perform tests to verify if a PRCC is significantly different from zero and if two PRCC values are significantly different from each other. Each PRCC (γ) generates a value T according to the following statistic [83]:

$$T = \gamma \sqrt{\frac{N-2-p}{1-\gamma^2}} \sim t_{N-2-p} \tag{7.3}$$

where t is distribution with $(N-2-p)$ degrees of freedom. N is the sample size and p is the number of inputs or parameters whose effects are not counted when the PRCC is computed. It is important to notice that eq. (7.3) is exact for linear partial correlation when the inputs and output are normally distributed, otherwise is a large-sample approximation. The extended Fourier amplitude sensitivity test ($eFAST$) is based on the original FAST [84]. eFAST was developed by Saltelli [85] and it is a variance decomposition method. The variance contribution of the input parameters to the model output is quantified by the calculation of the variance

$$s^2 = \frac{\sum_{i=1}^{N}(y_i - \bar{y})}{N-1} \tag{7.4}$$

where N is the sample size, y_i the model output and $\bar{y}$ the sample mean. Then the algorithm partitions the output variance by varying different parameters at different frequencies. The Fourier coefficients are used to compute the proportional variance contribution (*i.e.*, partial variance) of each input parameter which leads to variations in model output. The propagation of each parameter's frequency from input to the output, trough the model, gives a measure of sensitivity of the model to the parameter. We can describe then the eFAST method in three steps: first step is to generate random sample, then the model predictions are obtained, and, in the last step, Fourier coefficients and partial variances of the input parameters are calculated. The sampling procedure implemented within the first step defines the sinusoidal function x_i, $i = 1, \ldots, N_s$, called *search curve*, of a particular frequency ω_i for each parameter. The choice of the desired

search curves depends on the distribution of parameter values (*e.g.*, uniform, normal, lognormal, ...). We use the following from [86]

$$x_i = \frac{1}{2} + \frac{1}{\phi}\arcsin(\sin(\omega_i s + \phi_i)) \quad \text{for } i = 1, \ldots, N_s \tag{7.5}$$

where N_s is the total number of samples per search curve, given by

$$N_s = (2M\omega_{\max} + 1)N_r \tag{7.6}$$

M is the interference factor (usually 4 or higher), $\omega_{\max}$ is the largest among the set of ω_i frequencies and N_r is the number of curves used for the resampling obtained by introducing into each sinusoidal function *a random phase shift* ϕ_i uniformly chosen in $[0, 2\pi)$. The frequencies ω_i assigned to the parameters are chosen by several criteria and we refer the reader to the Table 2 in [86]. The minimum recommended value for N_s is 65 [86]. After this sampling step it is possible to obtain the model predictions with a total number N of model simulations given by

$$N = N_s \cdot k \cdot N_r \tag{7.7}$$

where k is the number of parameter analysed. The last step is to calculate the model sensitivity to each input parameter. The first-order sensitivity index S_i of a given parameter i is calculated as a fraction of the total variance as

$$S_i = \frac{s_i^2}{s^2_{\text{total}}} \tag{7.8}$$

where the variance s_i^2 is given by

$$s_i^2 = 2\sum_{j=1}^{+\infty} A_j^2 + B_j^2 \tag{7.9}$$

where A_j, B_j are the Fourier coefficients at the frequency of interest j. The S_i index describe the fraction of model output variance explained by the input variation of the ith parameter. The total-order sensitivity index S_{Ti} of a given parameter i is the following variance

$$S_{T_i} = 1 - S_{C_i} \tag{7.10}$$

where S_{C_i} is the summed sensitivity index of all parameters except i calculated by using their identification frequencies.

The main advantages of eFAST are its robustness and its computational efficiency.
It is important to notice that the PRCC and the eFAST procedures give the measure of two very different model properties. Specifically, PRCC provides a measure of monotonicity after the removal of the linear effects of all but one variable. In contrast, eFAST measures the fractional variance accounted for by individual variables and groups of variables. Both methods should be used to have a complete and informative US analysis.

7.3 US analysis of the stochastic immune model

We now study the robustness of the positive equilibrium point E_P of the deterministic model (5.1). As we did in Chapter 5, we investigate here the stability properties of the equilibrium point of the stochastic version and then compare them with the properties of the same equilibrium in the deterministic case. We perturb the system (5.1) by multiplicative noise, considering stochastic perturbations of white noise type, directly proportional to distances of the variables from the values of the positive equilibrium point $E_P = ({x_U}^*, {x_I}^*, b^*, {i_R}^*, {a_R}^*)$. The system (5.1) is extended to the following form

$$\begin{aligned}
\mathrm{d}X_U(t) &= (s_U - \alpha_1 X_U(t)B(t) - \mu_{X_U}X_U(t))\,\mathrm{d}t + q_1(X_U(t) - {x_U}^*)\mathrm{d}W_1(t)\\
\mathrm{d}X_I(t) &= (\alpha_1 X_U(t)B(t) - \alpha_2 X_I(t)A_R(t) - \mu_{X_I}X_I(t))\,\mathrm{d}t + q_2(X_I(t) - {x_I}^*)\mathrm{d}W_2(t)\\
\mathrm{d}B(t) &= \left(\alpha_{20}B(t)\left(1 - \frac{B(t)}{\sigma}\right) - \alpha_3 B(t)I_R(t) - \alpha_4 B(t)A_R(t)\right)\mathrm{d}t\\
&\quad + q_3(B(t) - b^*)\mathrm{d}W_3(t) \qquad (7.11)\\
\mathrm{d}I_R(t) &= \left(s_{I_R} + \int_{-\tau_1}^{0} w_1(\theta)B(t+\theta)\mathrm{d}\theta - \mu_{I_R}I_R(t)\right)\mathrm{d}t + q_4(I_R(t) - {i_R}^*)\mathrm{d}W_4(t)\\
\mathrm{d}A_R(t) &= \left(s_{A_R} + \int_{-\tau_2}^{0} w_2(\theta)B(t+\theta)\mathrm{d}\theta - \mu_{A_R}A_R(t)\right)\mathrm{d}t + q_5(A_R(t) - {a_R}^*)\mathrm{d}W_5(t)
\end{aligned}$$

where $q_i, \quad i = 1, ..., 5$, are positive constants and $W_i, \quad i = 1, ..., 5$, are independent Wiener processes.

The positive equilibrium E_P has also components that depend on both delays of the immune response. The study of the characteristic equation in the deterministic case leads to the conclusion that the positive equilibrium point E_P is asymptotically stable at $\tau_1 = \tau_2 = 0$. It is interesting to know which values of the delays let E_P undergo a

stability switch. By using the geometric stability switch criterion developed in 2002 by Beretta and Kuang [3], it was possible to study the presence of Hopf bifurcation with one delay and with the delay dependent coefficients. Unfortunately, the extension of this criterion to the case of two distinct delays is still an open problem. In [18] the authors performed a sensitivity analysis by applying a qualitative study of stability of switches in E_P by using a comprehensive sampling method known as Latin hypercube sampling (LHS). We implement an algorithm to perform uncertainty and sensitivity analysis of the stochastic model (7.11) and then compare the results obtained with the deterministic informations given by [18]. We use Matlab to implement the US analysis and perform our simulations.

7.3.1 eFAST results for the stochastic immune model

In the last chapter we noticed that the study of equilibria of the system (5.14) is affected by changes in the parameter values. A sensitivity analysis is useful to investigate the contribution of each parameter to the outcome of the model. We sampled eight parameters simultaneously $(X_U(0), I_R(0), A_R(0), \alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_{20})$, defining uniform pdfs for their distributions. We perform eFAST on the model (7.11). In figure 7.1 the parameters are varied according to a sinusoidal function as described in section 7.2.2. We set the total number of samples per search curve to $N_s = 65$ and we set the resampling size to $N_r = 5$ (for inference on S_i and S_{Ti}). Because of its peculiar sampling technique, eFAST must process the whole sampled data base and the sensitivity analysis results we obtained are valid only in the biological ranges given by Table 6.2. The indexes are evaluated at two different time points: $t_1 = 5000\Delta t$ and $t_2 = 10000\Delta t$.

The model output for the the sensitivity analysis is bacterial load. Tables 7.1 and 7.2 show the eFAST sensitivity indices. The two rows indicate the eFAST results at the two different time points t_1 and t_2. It is easy to notice that first order and total order eFAST values are not equal and it leads to conclude that interactions between parameters are relevant, *i.e.*, the model is not additive. Then for our conclusions about sensitivity results we use only using Table 7.2. Figure 7.2 shows the total-order indices S_{Ti} at time point t_1 for each parameter varied in eFAST.

The eFAST results suggest that the bacterial load levels are less affected by variations in the parameters α_1 and α_2, which are not involved in condition (5.4). Tables 7.3 and 7.4 show the coefficients of variation for first order and total order eFAST

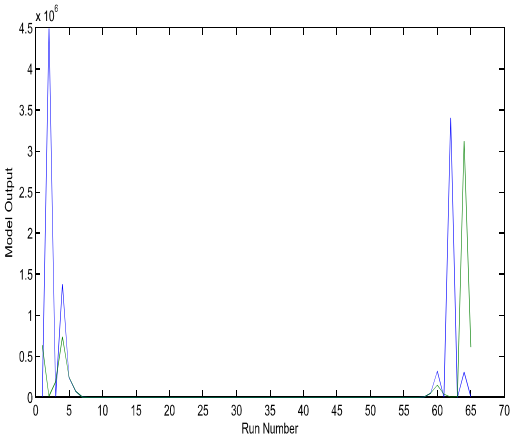


Figure 7.1: Model ouput for each parameter combination.

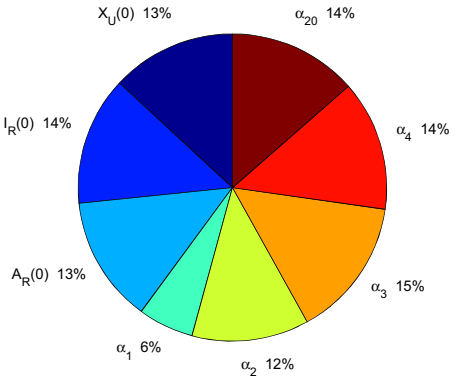


Figure 7.2: Bacterial load total order S_{Ti} for each parameter at time point $t_1 = 5000$ (percentages)

time	$X_U(0)$	$I_R(0)$	$A_R(0)$	α_1	α_2	α_3	α_4	α_{20}
5000	0.0588	0.1212	0.1196	0.0278	0.1053	0.2598	0.1263	0.1162
10000	0.1022	0.1187	0.0928	0.0761	0.1067	0.1604	0.1535	0.1197

Table 7.1: First order eFAST sensitivity indices at time points t_1 and t_2

time	$X_U(0)$	$I_R(0)$	$A_R(0)$	α_1	α_2	α_3	α_4	α_{20}
5000	0.8077	0.8358	0.8214	0.3595	0.7582	0.9066	0.8464	0.8354
10000	0.7766	0.8316	0.7162	0.6523	0.7933	0.8826	0.8082	0.8463

Table 7.2: Total order eFAST sensitivity indices at time points t_1 and t_2.

time	$X_U(0)$	$I_R(0)$	$A_R(0)$	α_1	α_2	α_3	α_4	α_{20}
5000	29.4143	60.1493	107.8046	85.9302	46.6951	43.5487	103.9439	28.1390
10000	33.5749	69.9412	105.0699	70.5396	46.8766	42.4009	89.0931	26.8142

Table 7.3: Coefficient of variation for first order eFAST sensitivity indices at time points t_1 and t_2.

time	$X_U(0)$	$I_R(0)$	$A_R(0)$	α_1	α_2	α_3	α_4	α_{20}
5000	9.4677	46.9370	61.7153	73.2096	35.4197	16.3166	82.5314	24.6107
10000	7.9457	51.0632	60.1596	65.7470	34.9027	15.3050	76.6768	22.6330

Table 7.4: Coefficient of variation for total order eFAST sensitivity indices at time points t_1 and t_2.

sensitivity indices, respectively. By comparison of the two tables we notice that the coefficients of variation are always larger for the first order than for the total order sensitivity indices. This result is in agreement with the informations obtained in [61].

7.3.2 LHS and PRCC results for the stochastic immune model

We adapt LHS method to investigate the existence of stability switches for the equilibrium point E_P. We know that the equilibrium point E_P depends on both delays τ_1 and τ_2 and that stability of E_P can be lost trough Hopf bifurcations occurring for several values of the delays. The delays are significant only when E_P exists, since LHS technique must process on the subset of samples satisfying condition (5.4). Then we sample only τ_1 and τ_2 in the ranges $[10^{-2}, 1]$ and $[5, 10]$, respectively, which are compliant with the intervals given in Table 5.1. In the matter of the other parameters we choose the combination of values given in Table 7.5, which satisfy the condition (5.4) for the existence of E_P. All the noise coefficients are keep constant at the same value, namely 10^{-2}. the initial condition is $\left(10^4, 1, 20, 10^3, 10^2\right)^T$.

We ran a total of 13000 simulations, given by 130 parameters combinations each one tested with 100 different Wiener processes (that is, 100 different random scenarios). The aim is to investigate how sensitive are the outcome of all the five equations to the variability in the delays. We sampled the PRCC coefficients and the variables at two time points, namely at the half and at the end of the time interval.

Name	Value	Name	Value
α_1	10^{-3}	σ	10^5
α_2	10^{-3}	μ_{X_U}	0.011
α_3	10^{-4}	μ_{X_I}	0.011
α_4	10^{-4}	μ_{I_R}	0.11
α_{20}	.5	μ_{A_R}	0.33

Table 7.5: Parameters values used for LHS sampling

	X_U		X_I		$B\|$	
time	τ_1	τ_2	τ_1	τ_2	τ_1	τ_2
5000	−0.2629	0.7989	−0.3672	0.8162	−0.4610	0.7958
10000	−0.3928	0.9109	−0.1874	0.9196	−0.6222	0.9310

	I_R		A_R	
time	τ_1	τ_2	τ_1	τ_2
5000	0.2588	0.7267	−0.3578	0.7213
10000	0.0347	0.9048	−0.5755	0.9347

Table 7.6: PRCC indices of all variables with respect to the delays, computed at two time points: at half and at the end of the time interval.

In Fig. 7.3–7.7 the corresponding scatter plots are shown, at the end of the time interval: it is clearly seen that in the investigated ranges, all the variables seems quite uncorrelated to the uncertainty in τ_1, while they are correlated to the uncertainty in τ_2. This is confirmed by the PRCC values reported in Table 7.6. Even if the PRCC analysis is more suitable to emphasize linear correlation and the plots with respect to τ_2 could well be linearly fitted, also a nonlinear correlation seems to be possible. This surely deserve additional investigations.

7.4 Biological discussion

Our analysis gives information about the best approach for the clearance of bacterial growth. The innate immune response plays a key role. A successful immune response is given by a rapid and strong innate response, since our study indicates that bacterial load is more affected by variations of baseline levels, as well as half-life of innate immunity

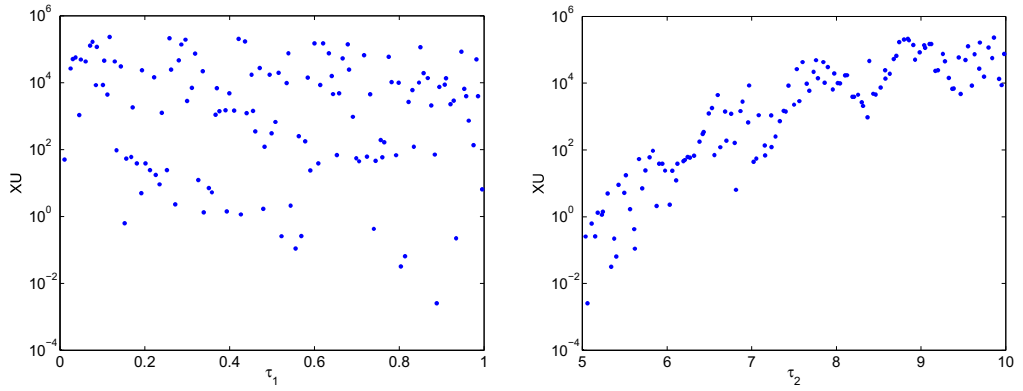


Figure 7.3: scatter plots of variable X_U (uninfected) with respect to the delays. The Pearson correlation coefficient is -0.19545 for τ_1 and 0.56235 for τ_2.

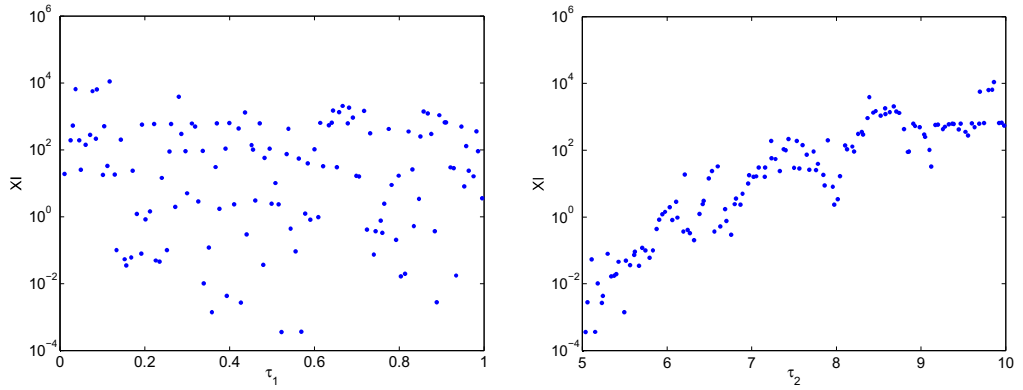


Figure 7.4: scatter plots of variable X_I (infected) with respect to the delays. The Pearson correlation coefficient is -0.30657 for τ_1 and 0.43329 for τ_2.

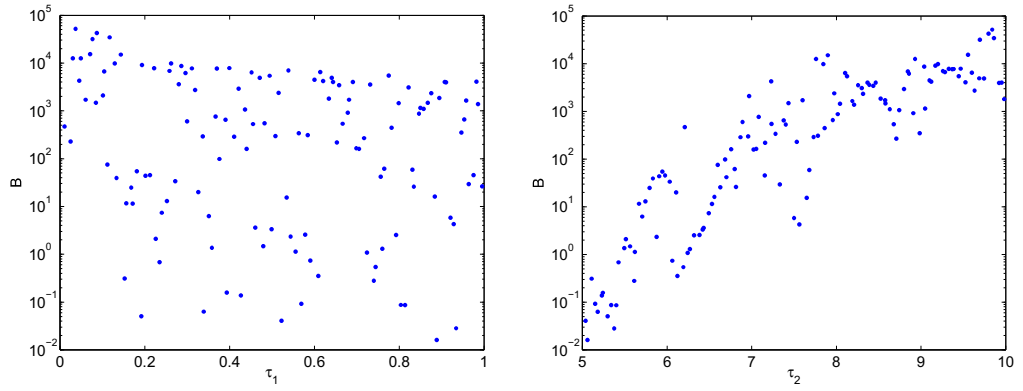


Figure 7.5: scatter plots of variable B (bacterial load) with respect to the delays. The Pearson correlation coefficient is -0.37033 for τ_1 and 0.51487 for τ_2.

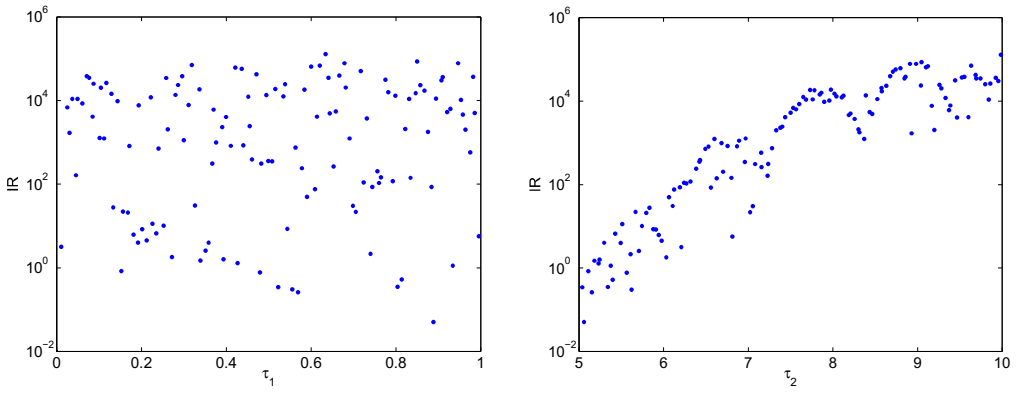


Figure 7.6: scatter plots of variable I_R (immune response) with respect to the delays. The Pearson correlation coefficient is 0.11543 for τ_1 and 0.62953 for τ_2.

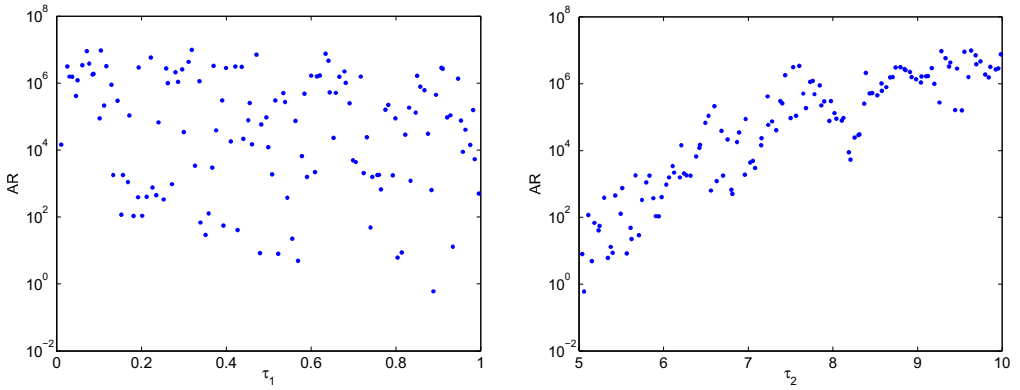


Figure 7.7: scatter plots of variable A_R (adaptive response) with respect to the delays. The Pearson correlation coefficient is -0.26561 for τ_1 and 0.6182 for τ_2.

cell turnover and bacteria killing by innate response than other values parameters. When innate response fails, the adaptive response is activated to kill or controlling the bacterial growth. It also happens if the innate response is very delayed. It is worth noticing that our analysis also suggests that a balance between the bacterial killing are affected more by adaptive response and the growth rate of bacteria is crucial. In fact, on one hand a very strong and rapid adaptive response can be very successful in clearing the infection, but in some cases it could lead to inflammations and tissue damage. On the other hand, if the bacteria growth is not controlled, it proliferates causing widespread inflammation. The infected steady state, given by E_P, represents the successful settlement of the host by bacteria and depends on the delay of innate and adaptive responses. With the uncertainty analysis we achieved a classification of suitable thresholds of the delays to predict stability switches of positive equilibrium point of our stochastic immune model. When τ_1 and τ_2 are smaller than the stability switches $\tau_{1(0)}$ and $\tau_{2(0)}$ respectively, then the infection can be stabilized. In fig. ? we can observe damped and sustained oscillations. From a biological viewpoint we have that the damped oscillations represent a latent infection where it was possible to reach a balanced coexistence between the host and the bacteria. Besides, sustained oscillations represent a chronic infection scenario where it is possible to observe an uncontrolled growth of bacteria. Two examples of applications of the presented model and analysis could be the intracellular bacterium Mycrobacterium tubercolosis [87], that usually infects the lung, and the herpes simplex virus (HSV), a virus infection of the skin.

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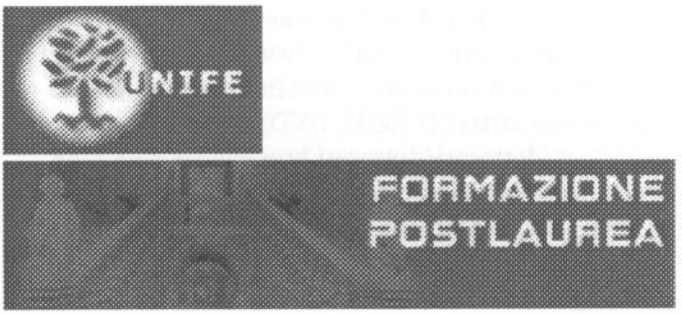

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